DOES NOT CIRCULATE

UNIVERSITY OF MICHIGAN
SEP 4 1952
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY AUGUST 16 1952

TABLE OF CONTENTS

Coronary Thrombosis and Its Response to Treatment A. RAE GILCHRIST, M.D., F.R.C.P. 351

Tuberculous Meningitis A. R. SOMNER, M.D. 356

Observations on the Laboratory Diagnosis of Tuberculous Meningitis
R. W. S. HARVEY, M.B., Ch.B. 360

Hypersensitivity, Stress, and Toxicity T. W. LEES, M.B., Ch.B. 363

Nematodes, Nervous Disease, and Neurotropic Virus Infection
J. R. M. INNES, SC.D., PH.D., and C. SHOHO, D.V.M. 366

Hereditary Methaemoglobinaemic Cyanosis ANTOINE CODOUNIS, M.D. 368

Methaemoglobinaemia Due to Nitrates in Well-water
W. A. B. CAMPBELL, M.D., M.R.C.P.Ed. 371

Cutaneous Reactions to Injection of Progesterone Solutions into the Skin
VERNON R. PICKLES, M.D. 373

MEDICAL MEMORANDA
Milk Allergy. W. F. WALKER, M.B., Ch.B. 374
Two Cases of Acute Idiopathic Porphyria. C. J. WILLIAMS, M.D., M.R.C.P., and K. R. LOTHIAN, F.R.C.S. 375

REFRESHER COURSE
The Surgical Relief of Pain. LAMBERT ROGERS, M.D., F.R.C.S. 383

GENERAL ARTICLES AND NEWS
The Control of New Remedies. Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., D.M., F.R.C.P. 385
Sir WILLIAM SAVAGE, 80 388
ORDER OF ST. JOHN OF JERUSALEM 389
HER MAJESTY'S HOUSEHOLD 390
UNIVERSITIES AND COLLEGES 398
MEDICAL NEWS 400
BIRTHS, MARRIAGES, AND DEATHS 401
QUESTIONS AND COMMENTS 401

REVIEWS
The Kidney 376
Surgeons' Experience 376
Nervous Conduction 376
Hygiene and Dietetics 376
E.N.T. Examination 377
Method in Medicine 377
Applied Physiology 377
Allergy Reviewed 377

LEADING ARTICLES
Treatment of Coronary Thrombosis 378
Epidemiology of Poliomyelitis 378

ANNOTATIONS
Tuberculous Meningitis 380
Medical Laboratory Technology 381
Methaemoglobinaemia 381
Restrictions on Hypnotism 382
Nursing at 18 382

REPORTS OF SOCIETIES
Second International Congress of Biochemistry 388

OBITUARY
Sir Jack Drummond, D.SC., F.R.S. 394
E. R. Garnett Passe, F.R.C.S., F.A.C.S., D.L.O. 397
H. E. Moore, O.B.E., M.B. 397

SUPPLEMENT
Full Contents on First Page of Supplement
The General Practitioner and the Local Authority. G. T. RUTHERFOORD, M.B., B.S., D.R.C.O.G. 97
Durham Dispute Ended 98
Working Party's Recommendations 98
Mileage Allowances for Hospital Medical Staff 98

CORRESPONDENCE
Confused Nomenclature. DENIS BROWNE, F.R.C.S. 390
Peptic Ulcer and the Neurotic. DORIS M. ODLUM, M.R.C.S.; D. STAFFORD-CLARK, M.D. 390
Danger from Cuffed Endotracheal Tubes. C. F. J. BARON, M.R.C.S. 391
Social Trends and Home Confinements. DUGALD BAIRD, M.D. 391
Symptomatic Purpura during Isoniazid Therapy. D. M. COLLINS, M.D. 391
Isolation and Quarantine. R. E. SMITH, M.B. 392
Death from Penicillin. J. A. HARPMAN, F.R.C.S.Ed. 392
Lithopaedion in African Women. R. B. LEECH, M.B. 393
Is Metallic Mercury Poisonous? A. H. KUTSCHER, D.D.S. 393
Chronic Lead Poisoning. A. W. GILKS, M.R.C.S. 393
Allergy and A.C.T.H. JACK CARR, M.R.C.S. 393
Trapping the Surgeon's Sweat. N. STRATON, L.D.S. 393
Accidental Generalized Vaccinia. MARY L. ASSINDER, M.B. 394
Gall-stone Colic. T. M. FURBER, M.B. 394

Vital Statistics 398

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4780, WEEKLY, PRICE 2/-

Copyright

REGISTERED AS A NEWSPAPER

Ralgex

ANALGESIC - RESOLVENT
COUNTER-IRRITANT

A solid embrocation without disagreeable odour. Will not stain clothing.

Indications	Action
RHEUMATIC AND MUSCULAR PAINS, NEURALGIA AND HEADACHES, BRONCHITIS, CATARRH, LARYNGITIS	*The analgesic properties in Ralgex afford rapid relief of all rheumatic and other pains.* *Ralgex acts as a counter-irritant in cases of Bronchitis, Catarrh, Laryngitis or Pharyngitis.*

Clinical samples and literature gladly sent upon request.

PHARMAX LIMITED
The Organ Works, Old Hill, Chislehurst, Kent

a PHARMAX product

SURGICAL SERVICE SALTAIR

SALT & SON LTD.
— for —

SURGICAL BELTS and CORSETS to individual measurements
ELASTIC HOSIERY in all Thread Elastic qualities
TRUSSES for all types of hernia, to individual requirements
ORTHOPAEDIC APPLIANCES
ARTIFICIAL LIMBS, etc., etc.

An Invitation

Our services are available free of charge to the Medical Profession in carrying out work of an experimental nature for any new type of surgical support.

LONDON ADDRESS FOR APPOINTMENTS:—
1. STANLEY HOUSE. 103. MARYLEBONE HIGH ST.
LONDON. W.1. TEL: WELBECK 3034.

HEAD OFFICES:
BIRMINGHAM, 2

Delicious fruit drinks for Diabetics

ROSE'S
DIABETIC LIME JUICE
3/6 *a bottle*

ROSE'S
DIABETIC LEMON OR ORANGE SQUASH
3/- *a bottle*

All specially prepared without added sugar

FROM HEALTH FOOD STORES AND LEADING CHEMISTS

EPHAZONE tablets
Rational, symptomatic treatment in Asthma & Bronchitis

Each tablet contains Ephedrine, the important antispasmodic for bronchial spasm, Theobromine, for its relaxing effect on the bronchial muscle and for stimulation of the coronary circulation, Phenazone, for its soothing effect on the higher centres, and Calcium gluconate, a readily absorbable calcium salt, for diminishing capillary permeability and checking the secretion of mucus.

These active ingredients with complementary effects in bronchial asthma are presented in the following proportions in the 'EPHAZONE' Tablet:

Ephedrine hydrochloride	**¼ grain**
Theobromine	**¼ grain**
Phenazone	**1 grain**
Calcium gluconate	**¼ grain**

This preparation is sanctioned for prescription under N.H.S. Please write for samples and descriptive leaflet.

EPHAZONE LTD. 59 BROOK ST., LONDON, W1. TEL: MAYFAIR 5496

BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 16 1952

CORONARY THROMBOSIS AND ITS RESPONSE TO TREATMENT*

BY

A. RAE GILCHRIST, M.D., F.R.C.P.

Physician, the Royal Infirmary, Edinburgh; Reader in Clinical Cardiology, University of Edinburgh

In its power to strike down those in the prime of life, coronary thrombosis, by its increasing frequency, may be regarded as the oustanding malady of our time. Thirty years ago it was a rarity even in pathological experience. To-day we count our cases in hundreds and pass on to the next.

Over these years diagnosis has been in the forefront, to the neglect of therapy. So it is that with instrumental aid the recognition and localization of the myocardial infarct have become progressively more and more refined. Only within the last few years has any material advance been made in the management of the patient stricken with so grave a malady. It is satisfactory to record at the outset that the days of "masterly inactivity" are being gradually replaced by a positive therapeutic programme which has halved the mortality rate and which opens the way to further endeavours on behalf of these patients.

Diagnosis

Before considering present trends in the treatment of the acute phase of the illness it is necessary to have in mind the clinical features of this particular form of coronary disease so that it may be distinguished from its immediate associates. Amongst many clinical entities there are at least three which have coronary sclerosis as a common denominator and require clarification.

Midway between the transient myocardial ischaemia of angina pectoris and the major attack of coronary thrombosis stands a group of cases notable for the ease with which spontaneous cardiac pain occurs at rest—pain longer and severer than the usual attack of effort angina and yet not as severe as the clear-cut episode of coronary thrombosis. To this group, so ably and clearly differentiated by Master (1947) and Master *et al.* (1949), the term "acute coronary insufficiency" is applied. The usual attack of angina pectoris is a manifestation of a temporary and local oxygen lack, too transient to imperil the muscle cells; acute coronary insufficiency is a severer grade of the same process which, when prolonged, leads to a diffuse myocardial asphyxia resulting in a speckled patchy necrosis, subendocardial in distribution. By contrast, acute coronary thrombosis leads to abrupt interruption of blood flow with the formation of a circumscribed myocardial infarct.

Few practitioners can be unfamiliar either with the dramatic onset and treacherous course of the fully developed syndrome of coronary thrombosis or with its equally common but often deceptive variants. Prolonged substernal pain, a greater or less degree of shock, and signs of tissue destruction are the main components of a clinical picture all too common. When pain is not excruciating or prolonged, shock in greater or less degree is an indication of the seriousness of the situation. The diagnosis is supported by the discovery of tachycardia, a feeble apical impulse, poor-quality heart sounds, a falling arterial pressure, and a triple rhythm. Shock and exhaustion may overshadow the pain, respiratory distress increase, and signs of left ventricular failure develop readily. Tissue necrosis accounts for the prompt leucocytosis, the febrile reaction, the increase in urinary urobilinogen (Focht and Hanson, 1948), the disturbance of the sedimentation rate, and the sequence of changes in pattern observed in serial electrocardiograms. The main features aiding diagnosis, as encountered in the severer grades, are presented in Fig. 1.

Minor attacks of coronary thrombosis are even more commonly encountered. They are readily mistaken

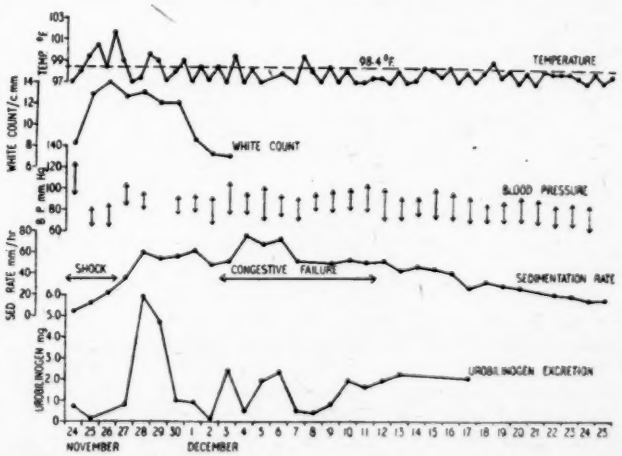


FIG. 1.—Showing from above downwards the day-to-day response of the temperature, white-cell count, blood pressure, erythrocyte sedimentation rate, urinary urobilinogen excretion, after an acute coronary thrombosis sustained by a man aged 57 on the day of his admission to hospital. A polymorph leucocytosis precedes and accompanies the rise in temperature. The blood pressure falls to shock levels. A gradual increase in the sedimentation rate reaches a maximum 11 to 13 days after the infarction, when the white-cell count has returned to normal. A sharp increase in urobilinogen excretion occurs on the fifth day of the disease—a sign sometimes helpful in distinguishing the myocardial infarct from other forms of angina (Focht and Hanson, 1948). Shock persisted for three days and was followed by congestive heart failure six days later. The patient made a good recovery on anticoagulant therapy.

*Based on an address given to the Cardiff Medical Society on April 9, 1952.

for acute coronary insufficiency. The patient already handicapped by angina pectoris is always suspect. Any unusual, unexpected, or unprovoked attack of his pain may well prove to be an actual occlusion, if not premonitory of a major disaster in the immediate future. To establish the diagnosis of infarction a search should be made for signs of tissue destruction, and among these the practitioner, when other laboratory methods are denied to him, will find helpful the long-sustained disturbance of the sedimentation rate. The readings commonly reach a maximum by the end of the second week and do not return to normal for four to eight weeks. By this procedure a clue to the diagnosis can often be reached in retrospect (Fig. 1).

It is well known that a myocardial infarct may occur painlessly (Rinzler, 1951 ; Papp, 1952). Shock and fever are not invariably present. The clinical pattern of acute infarction therefore varies greatly, but an undisturbed sedimentation rate after such an episode must be very exceptional: it is a valuable diagnostic procedure, easily applied and readily repeated. Every attack of cardiac asthma or sudden and acute pulmonary oedema should suggest the possibility of an acute infarction. Sudden syncopal attacks or giddiness, particularly if followed by prostration, residual exhaustion, and general bodily weakness, can often be explained on a similar basis. Nocturnal dyspnoea with insomnia and restlessness in the elderly should never be lightly dismissed. It is in these instances that the application of the clinical procedures outlined in Fig. 1 may help to clarify the diagnosis, even when a twelve-lead electrocardiogram—the usual court of appeal—is equivocal.

Response to Anticoagulants

After five years' personal experience of the use of anticoagulants in the treatment of coronary thrombosis, the time is appropriate for a stock-taking of results. In an illness of the gravity of coronary thrombosis an adequate test of the efficacy of a remedy can be found in comparative studies of mortality rates amongst a series of treated patients presented side by side with adequate controls. Of 1,800 patients observed at various centres the death rate among those receiving anticoagulants during the first few weeks of the illness was 16.2%, as compared with 30.6% in the controls. Similarly, the incidence of thrombo-embolic phenomena amongst the same large series of patients fell from 21.8% to 9% in the treated groups (Tulloch and Gilchrist, 1951). There is little doubt that the employment of anticoagulants in the first few weeks after an acute coronary thrombosis marks a distinct advance in treatment.

Apart from statistical proof, an effective remedy influences the pattern of the disease, the recovery process, and the frequency and severity of the major complications. In this respect anticoagulants in coronary thrombosis are no exception. A study of their influence on the course of the more acute phase of the illness reveals beneficial effects more widely dispersed than hitherto suspected. Moreover, the successful application of these remedies opens the way for further therapeutic endeavours.

Material for Study

Our experience is based on a consecutive series of 318 patients confined to hospital practice. In general the hospital receives a selected group composed of the moderately severe or complicated cases. All grades of severity may be encountered, but many patients die immediately or within an hour or two of the onset and hence fail to be included in a hospital series. Some of the milder attacks occur in patients who never seek hospital care. Thus hospital experience, while a reasonably large sample, is not necessarily representative of the general community as a whole. Further, the character of the hospital clientele varies in different localities. In Edinburgh nearly 60% of patients suffering from acute coronary thrombosis reach the wards within 48 hours of the onset of the attack. As a result, our experience tends to be weighted with severe and commonly fatal cases. Similarly, in those surviving the first 24 to 48 hours serious complications are common.

One group, composed of a consecutive series of 161 patients, received treatment along the usual conservative lines, consisting of rest in bed for four to six weeks, analgesics and mild sedatives when necessary, a low-calorie diet, and simple symptomatic measures for such complications as arose. These patients received no particular remedy. The last 84 of the 161 consecutive patients in this series formed a small simultaneous control for a series of 70 patients treated in the same way but with the additional use of the anticoagulant dicoumarol. On this basis it was possible to substantiate the claims made for the beneficial effects of heparin and dicoumarol (Tulloch and Gilchrist, 1950). Since then our experience has been enlarged by a further study of the use of "tromexan" in the treatment of 87 consecutive patients (Tulloch and Gilchrist, 1951). A total of 157 consecutive patients have therefore been treated with anticoagulants, but only the dicoumarol group is supported by a simultaneous and strictly comparable control series. Thus the present studies are based on 161 conservatively treated patients and 157 receiving either dicoumarol or tromexan.

Use of Anticoagulants

Anticoagulant therapy was begun on admission to hospital, unless some serious contraindication to its use was discovered. Of these, peptic ulceration and cirrhosis of the liver are the two most likely to be encountered among coronary patients. Heparin is begun as soon as the diagnosis is established. It is given at six-hour intervals in a dose of 10,000 units (77 mg.) by interrupted intravenous injection during the day and by intramuscular injections during the night, usually for the first 36 to 48 hours, depending upon the degree of reduction in the prothrombin time produced by the simultaneous action of the oral anticoagulant.

Tromexan proves to be an efficient substitute for dicoumarol and has the advantage that its daily dosage is more easily regulated. It is quicker and shorter in action, safer in use, and equally efficient (Tulloch and Gilchrist, 1951). The total quantity administered on the first day of treatment is 1,200 mg., and on the second day usually 900 mg. The prothrombin content of the blood, which is the guide to further dosage, is estimated each day about 9 a.m., after a light breakfast. The heparin injections are discontinued when the morning prothrombin time reaches 35 seconds or more. Tromexan is employed daily for 28 days after the onset of the infarction or for 21 days after the last thrombo-embolic complication, whichever is the longer. The aim is to maintain the patient's prothrombin time at a level two to two and a half times the control reading for that day in the laboratory. The quantity of tromexan administered for each day's treatment is gauged from the reading of the patient's prothrombin time, determined on that particular morning. Individual requirements vary greatly, and on occasion the prothrombin time may fluctuate through a wide range from day to day in the same patient. As a general rule a maintenance dose of 1½ to 2½ tablets (450 to 750 mg.) is about the average daily quantity required to hold the morning prothrombin time within the therapeutic range, but the requirements of different patients vary enormously.

Satisfactory maintenance of the prothrombin time within the therapeutic range is shown in Fig. 2. In this particular patient the daily dose of tromexan was reasonably steady. On only one occasion, the twelfth day, did the morning prothrombin time fall below the desired level. By way of

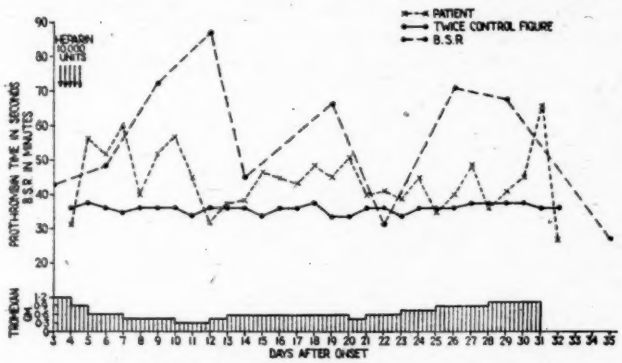


FIG. 2.—Showing the response of the prothrombin time to the daily adjustment of the tromexan dosage. The intention is to maintain the patient's morning prothrombin time at a value slightly greater than twice the control figure for that day. In this patient the daily tromexan dose was reasonably steady, only minor fluctuations being observed in the prothrombin times. (Reproduced from *American Heart Journal* (Tulloch and Gilchrist, 1951), by permission of the editor and publishers.)

contrast, Fig. 3 illustrates wide fluctuations in the prothrombin time, which can prove more harmful to the patient than a moderately sustained hypoprothrombinaemia. Many factors are known to influence the response to the coumarol compounds, particularly the state of the alimentary tract. A reduced food intake, even for a few days, acute and chronic alcoholism, and the simultaneous use of a gut-sterilizing antibiotic (Wright, 1952), such as "aureomycin" or chloramphenicol, are among the factors which seem to increase the patient's sensitivity to the coumarol compounds.

With adequate laboratory control, haemorrhagic complications are usually trivial, taking the form of a mild epistaxis, melaena, or haematuria. A haematemesis and a pontine haemorrhage contributed to death in two instances. Treatment of bleeding consists in the temporary interruption of the anticoagulant and the administration of vitamin K, 50 mg. intravenously. Blood transfusion was required on only one occasion.

Results of Treatment

The favourable influence of anticoagulants on the outcome of the disease in this series of patients is emphasized by the reduction of the mortality rate over the first six weeks of hospital care from 42.2% in our conservatively treated group to 20.4% among those receiving anticoagulants. Similarly, only 38% of the control patients ran a course free of one or more of the four major complications—shock, congestive heart failure, thrombo-embolic episodes, or sudden death—whereas in 51% of those receiving anticoagulants the illness was uncomplicated by any major episode.

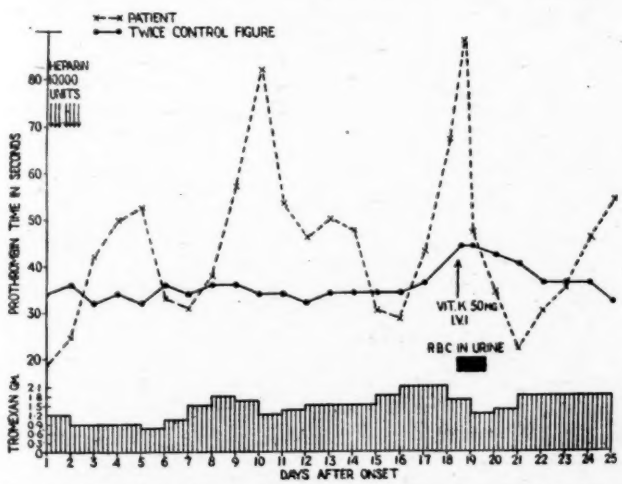


FIG. 3.—Showing wide fluctuations in the morning prothrombin time. This patient required a high average dose, which was difficult to adjust. The abrupt climbs in the prothrombin times suggest a delayed response to tromexan with accumulation thereafter. Abrupt fluctuations in prothrombin time are harmful and are commonly associated with complications. Haematuria occurred on the eighteenth and nineteenth days. (Reproduced from *American Heart Journal* (Tulloch and Gilchrist, 1951), by permission of the editor and publishers.)

It has often seemed that both the dicoumarol-treated and the tromexan-treated patients, particularly the latter, look better and feel better from an earlier stage in the illness than do the controls denied this form of therapy. Even the severely shocked patient will commonly show within a few days of the start of treatment a return of colour to the cheeks, a fresher expression, a general look of well-being, and an increased confidence, not often encountered at the same stage of the illness amongst the conservatively treated. On these grounds alone it would be reasonable to suspect that tromexan conferred benefits other than those directly concerned with prolongation of the clotting mechanism.

Course of Illness.—A study of the course of the illness indicates that major complications are apt to occur in a definite sequence and on occasion can be anticipated. For instance, as shown in Fig. 1, an onset accompanied by shock in a severe or protracted form is, if survived, commonly followed even within a few days by the development of congestive heart failure. The recovery process is punctuated by a succession of major and minor hurdles, each a test of cardiac reserve and therapeutic management. The first hurdle is shock, at which a stumble may be said to predispose to a fall at the next jump, heart failure. Throughout the course thrombo-embolic episodes are an ever-present danger, and not until four weeks have elapsed are the immediate risks surmounted.

Complications

The accompanying Table illustrates the frequency of the main complications and their influence on the mortality rate of the first six weeks of hospital care. Approximately 43% die in the control series and 21% in the treated. The notable features are the reduction in deaths from shock and from thrombo-embolic episodes in those treated with anticoagulants.

Incidence and Mortality Rates of the Four Major Complications of Acute Coronary Thrombosis as Observed During the First Six Weeks among a Group of Conservatively Treated Patients as Compared with a Corresponding Group Receiving Anticoagulants

Complication	Control Group			Anticoagulant Group		
	Incidence	Deaths from All Causes	Deaths from the Complication	Incidence	Deaths from All Causes	Deaths from the Complication
Shock	29%	24%	15%	20%	10%	4%
Heart failure	29%	20%	13%	33%	20%	13%
Thrombo-embolic incidents	28%	15%	10%	10%	7%	1%
Sudden deaths	5%	5%	5%	3%	3%	3%
Deaths			43%			21%

Thrombo-embolic Incidents

It is natural to consider first the influence of anticoagulants on the incidence of thrombo-embolic episodes, which prove to be a more frequent and serious complication of acute myocardial infarction than is commonly realized. A recurrence of thrombosis in an additional coronary branch, or an extension of the original thrombus to involve an adjoining arterial twig, is a frequent and serious happening. The occlusion of a systemic artery as a result of detachment of intraventricular clot, or the development of peripheral phlebothrombosis in the calf veins or elsewhere with resulting pulmonary infarctions, as single or multiple episodes, are examples of the risks to which these patients are exposed during the first few weeks. Death from this cause usually occurs before the fourth week. As shown in the Table, the

frequency of this complication is reduced from 28% to 10%, and deaths directly attributable to this cause fall from 10% in the control group to 1% in the treated. Wright and his colleagues (1948) concluded that anticoagulants reduced the death rate at each week of the illness. Unless anticoagulants are begun within the first 24 to 48 hours, occasional thrombo-embolic episodes cannot be avoided, as there is always the risk of detachment of clot from the thrombus already formed on the intraventricular endocardium overlying the infarct. An occasional embolic death is therefore bound to occur, but with early and efficient treatment over the first four weeks deaths from this cause can be reduced to negligible proportions.

Shock

This complication is so common as to constitute in many instances an important diagnostic feature differentiating infarction from other causes of cardiac pain. It varies greatly in degree, being occasionally absent in some patients and serious enough to cause death in others. In an admittedly arbitrary fashion the grade of shock has been classified on a purely clinical basis as severe, moderate, and mild or absent.

The importance of this outstanding complication of the illness can be judged from the fact that the severe grades carry a mortality rate exceeding 80% within six weeks of the onset of the attack, whereas only 25% of patients die when shock is moderate, mild, or absent. Similar findings have been reported by Mintz and Katz (1947) and by Epstein and Relman (1949).

The Table shows that the incidence of the severer grades of shock was 29% in the control and 20% in the treated series. Admittedly, the numbers available for analysis in this subgroup are small and must not be overemphasized, yet the discovery that only one-fifth of the severely shocked patients (4 in 20) died from this cause in the treated group as compared with approximately half those in the control (15 in 29) suggests that the early and efficient use of heparin and tromexan may have a favourable influence on the outcome of the shock syndrome. In support of this probability clinical experience indicates that an increase in the severity of the shock state after treatment with anticoagulants has been started is exceptional. Furthermore, the Table indicates that the overall reduction in the mortality rate among those receiving anticoagulants cannot be due solely to a decrease in frank thrombo-embolic deaths. It seems probable that the prompt and energetic use of anticoagulants contributes to the reduction in mortality rate by decreasing the deaths from shock.

By way of explanation for this finding it may be suggested that the early employment of heparin supplemented by tromexan may limit the spread of multiple thrombotic extensions in and through the zone of demarcation separating the necrotic from the adjoining healthy muscle. The hypotension of profound shock favours further thromboses in the coronary distribution, in the periphery, and subsequently in the pulmonary circuit. A succession of minor thrombotic episodes of this nature, perhaps insufficient in themselves to yield localizing signs, will tend to perpetuate the state of shock and favour an extension of the original infarct. By controlling the thrombotic tendency anticoagulants may thus limit the extent of the original infarct, save uninfarcted muscle, and thereby prevent an advance in the vicious circle of thrombosis, infarction, and hypotension.

Heart Failure

Some degree of left ventricular failure, as demonstrated by signs of moisture in the lungs, is very common after a myocardial infarct. When unaccompanied by any symptoms of respiratory distress such minor examples of cardiac failure have not been included in this analysis. Early signs of right-sided failure often consort with left ventricular failure. Both have been included under the heading of heart failure when symptoms attributable to this cause were in evidence. Approximately 29% of the patients developed frank signs and symptoms of one or other form of heart failure within six weeks of the onset. In about half the cases failure was of the left ventricular type. In the remainder a greater or less degree of right-sided failure was also present. The incidence was a little greater in the treated groups.

Had the incidence of severe shock been as heavy in the treated group as in the controls, then with larger numbers surviving the early days of the illness it would be natural to suppose that the proportion showing signs of congestive failure in subsequent weeks might well have exceeded the incidence of 33% recorded among those receiving anticoagulants. In the groups, as they exist in this series of patients, there is no evidence to support the view that anticoagulants reduce the incidence of congestive failure or the deaths attributable to it. Indeed, the reverse may prove to be true.

Sudden Death

On the assumption that a proportion of the sudden deaths observed in the weeks after a coronary thrombosis are attributable to thrombo-embolic episodes of one kind or another, it is reasonable to expect a small reduction in the death rate from this cause among those receiving anticoagulants. The actual figures show a fall of from 5% amongst the controls to 3% amongst the treated.

Further Therapeutic Requirements

It is therefore apparent that the efficient use of anticoagulants makes a substantial contribution to the patient's welfare and his ultimate recovery. The conquest of one of the major complications—the thrombo-embolic episode—naturally leads to a consideration of the others in the hope that measures as effective for their prevention and treatment may be forthcoming.

It is clear that if further advances in treatment are to be made more attention must be devoted to the practical problems involved in the prevention and treatment of the severer grades of shock and congestive heart failure. With the risks of thrombo-embolic episodes controlled, these are now the outstanding causes of death. In this disease shock and congestive failure are essentially manifestations of myocardial damage. They may overlap in some degree, but shock is the primary event in the first 24 to 48 hours. Congestive failure may be present from the beginning or become manifest a few days later, but if the original shock is mild or of short duration congestive failure may never appear. The patient should then make a good recovery. It appears that protracted shock, if survived, predisposes to a greater or less degree of congestive failure at an early date. The latter can therefore be anticipated on occasions and appropriate therapeutic measures taken in advance. There are good grounds for believing that the prompt and efficient treatment of cardiogenic shock may well be the means of preventing the subsequent development of congestive heart failure.

Mechanics and Treatment of Shock

Although the clinical picture is similar to that seen after mutilating trauma or profuse haemorrhage, the mechanism of the production of shock in coronary thrombosis centres round the abrupt destruction of a portion of left ventricular muscle. Survival depends on the integrity of the remaining myocardium. In cardiogenic shock the acute hypotension is attributed to sudden left ventricular weakness associated, probably through reflex nervous channels, with a decreased peripheral resistance in the deeper organs and tissues. Coronary flow, depending largely on diastolic pressure, is correspondingly reduced, and possibly diminished further by vasoconstriction throughout the entire coronary tree.

The healthy myocardium suffers as a result of shock. Hypotension, whatever its origin, can produce significant ischaemia of large areas of myocardium and lead to degenerative fatty change and an irregular patchy cellular necrosis (Mallory, 1949–50; Melcher and Walcott, 1951). Hypotension in the coronary circuit favours myocardial

depression and defective flow in the intercoronary anastomotic channels, with ballooning of the infarcted area and of the surrounding myocardium under experimental conditions (Corday *et al.*, 1949), and shock, no matter how produced, may lead in elderly patients, and particularly those the subjects of coronary sclerosis, to the development not only of single but often of multiple fresh coronary arterial occlusions (Blumgart *et al.*, 1941). A reduced cardiac output is an essential feature, but, in contradistinction to the other forms of shock in which venous return is reduced, it is not uncommon to find in the severe shock of coronary thrombosis evidence of pulmonary congestion—a sign indicative of a venous return in excess of that which the left ventricle can accommodate. Cardiogenic shock is an entity of considerable complexity (Boyer, 1944).

Aggravating factors are well known. Treatment must be directed to the relief of the overpowering pain. Anxiety, fatigue, exposure to cold, excessive sedation, and the fluid loss of profuse sweating, vomiting, or haemorrhage may all have a detrimental influence. Morphine, oxygen, warmth, and reassurance are the first considerations in the correction of shock.

With a mortality rate in excess of 80%, the criticism that the acute hypotension of the severer grades of shock is salutary and relieves the work of the heart can be dismissed. Shock demands energetic treatment. The object is to maintain from the outset an adequate head of pressure in the aorta and thereby ensure a blood supply to the uninfarcted muscle generous enough to maintain its maximum efficiency. The risk of the extension of irreversible myocardial damage should thus be minimized or avoided.

It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date. Other vital organs will receive corresponding benefit with improvement in their blood supply. While the level of the blood pressure is not in itself a measure of the severity of the state of shock, yet it would seem advisable to maintain the systolic pressure at a figure greater than 100 mm. in those previously hypertensive and certainly over 90 mm. in the remainder.

In the worst situations the myocardium is shattered by the extent of the initial damage, and therapy will prove unavailing. The degree of shock is not, however, a reliable guide to the extent of the infarct, and it is therefore fair to assume that the employment at the outset of energetic measures may save enough myocardium to permit recovery in a proportion of the most gravely ill patients who might otherwise be expected to die within the first two or three days of the illness. These considerations allow of a therapeutic approach from various angles.

Pressor Drugs

There is a place for the pressor drug, which increases peripheral resistance and augments coronary flow, without stimulating metabolism, decreasing cardiac output, or initiating serious arrhythmias. Adrenaline, which increases myocardial excitability, is unsuitable, but various other pressor amines are under trial at the present time and encouraging results are being reported. Brams (1948) recommends desoxyephedrine in 5-mg. doses intravenously at short intervals with a sustaining intramuscular injection of 10 mg. later. Ephedrine, 35–70 mg. diluted in 100 ml. of 5% glucose in water administered intravenously over a period of two hours, has been employed (Hellerstein and Brofman, 1951), after which the pressor effect may be maintained by intramuscular injections of ephedrine, 25–30 mg. at intervals of two or three hours. *Nor*adrenaline (Barnett *et al.*, 1950; Goldenberg *et al.*, 1949), by intravenous infusion, elevates systolic and diastolic pressure without a quickening of the heart rate. It can be very effective in the emergency of an acute infarct, and has the advantage that the pressure level, which is very sensitive to alterations in the infusion rate, can be readily adjusted. Brofman *et al.* (1950) and Brofman (1952, personal communication) have had encouraging results in 18 severely shocked patients treated with mephentermine (methyl desoxyephedrine) given intravenously in an initial dose of 5–15 mg., the blood pressure being thereafter maintained by a slow drip at a rate of 10–70 mg. an hour, depending on the response. Of these patients, 14 emerged from the state of shock and 7 recovered sufficiently to be discharged from hospital in good health. Until further experience has been gained from the use of these drugs more definite recommendations cannot be made. They are certainly worthy of extended trial.

Transfusions

In haemorrhagic and traumatic shock transfusion has long been the mainstay of treatment. The obvious dangers of overloading the pulmonary circuit, and thereby adding to the embarrassment of a heart already overburdened, has resulted in a natural hesitation to employ this method in the presence of cardiogenic shock. Nevertheless, in selected cases transfusions of blood or plasma are occasionally beneficial (Epstein and Relman, 1949; Sampson and Singer, 1949). Experimentally, Corday *et al.* (1949) found that after coronary ligation the transfusion of heparinized blood restored the contractility of the ischaemic region around the infarct, raised the blood pressure, and decreased local cyanosis as a result of enhanced flow through the collateral circulation. There are therefore good physiological reasons for attempting to correct shock and low blood pressure by this means. Under clinical conditions the benefits of intravenous transfusions are less striking, the response being limited by the slow rise in arterial pressure and by the development of pulmonary oedema, a complication difficult to avoid in the presence of an increasing blood volume and a failing heart.

For the reason that hypotension can be more rapidly corrected by intra-arterial infusion, using little more than half the quantity of blood required when the intravenous route is employed, this method of treatment suggested by Page (1949) has been employed recently by Berman and Akman (1952), but without great benefit. While maintained, the infusion, delivered at a pressure in excess of the patient's diastolic reading, acts as an auxiliary heart (Page, 1949) and under experimental conditions leads to a retrograde flow through the aorta to the renal, coronary, and medullary arteries. If by this method aortic pressure can be maintained for some hours above the shock level without overloading the heart, an increased coronary flow should limit the area infarcted and support the surviving myocardium. Until the indications have been more precisely defined and the technique has been perfected to maintain the pressure at optimum levels, which at present are unknown, intra-arterial infusion is likely to be restricted to a limited number of desperately ill patients. Pressor drugs both on theoretical and on practical grounds appear to be a more rational form of therapy.

Digitalization

In the treatment of traumatic or haemorrhagic shock digitalis is valueless, but there are strong arguments in favour of its employment in cardiogenic shock when signs of left ventricular failure begin to develop. On theoretical grounds there has been a disinclination to use digitalis in the presence of a recent infarct lest it should favour rupture of the ventricle, induce serious arrhythmias, or enhance the clotting tendency and with a more powerful systole dislodge cardiac thrombi within the arterial system. It is probable that such accidents are as common when digitalis is not in use, but, should the danger seem real, quinidine or procaine amide may lessen the risks of the arrhythmias and anticoagulants may safeguard the patient from thromboembolic episodes. Rupture of the ventricle is uncommon before the end of the first week, by which time the stage of shock is past.

In severe cardiogenic shock the use of "digoxin," 1 mg. intravenously, is therefore justifiable, after which its oral

use may be recommenced in 12 to 24 hours. It is well recognized that digitalis poisoning readily occurs in elderly people with badly damaged hearts, and therefore careful supervision is all the more necessary.

Treatment of Congestive Heart Failure

The development of congestive heart failure within the first few weeks of a coronary thrombosis is regarded as a sign of ill omen. Its occurrence can often be anticipated and measures taken accordingly, for the more severe and the more protracted the initial shock the more probable is the early development of congestive failure.

Treatment should be directed to forestall the development of this serious complication. If digitalis has been used in the correction of the shock phase it should be continued in gentle doses for at least a week or two thereafter in the hope that the efficiency of the uninfarcted muscle may be maintained and enhanced. Bedford (1939) has noted the value of mercurial diuretics in acute left ventricular failure when oedema is confined to the pulmonary circuit.

After a coronary thrombosis, if moisture in the lungs persists for more than a few days or threatens to increase, digitalis and mercurials can be used cautiously, and even energetically should there be any hint of dyspnoea at rest. By so doing the formidable difficulties of advanced congestive failure, which is apt to develop rapidly in the week or two following recovery from the shock phase, can be eased or prevented and the patient guided through a treacherous stage of the recovery process in greater comfort. The importance of adequate rest and sound sleep during the early days of the illness cannot be over-emphasized, and there is no doubt of the value of a low-calorie diet, small meals, and simple salt restrictions.

It therefore seems that if a further advance is to be made in the treatment of the acute myocardial infarct the prompt correction of shock and the early adoption of measures to prevent the development of congestive heart failure are aspects worthy of more attention. The more adequate treatment is in the early days of the illness the greater the prospects of recovery.

Summary

Active measures in the treatment of acute coronary thrombosis are now yielding better results than ever before, even in the most gravely ill patients.

The employment of anticoagulants is an outstanding contribution to the treatment of this disease. By their efficient use the death rate over the first six weeks can be halved.

The dangers of thrombo-embolic complications can be reduced to negligible proportions.

Moreover, it appears that the prompt use of anticoagulants exerts a favourable influence on the outcome of the shock syndrome. Deaths from shock are less frequent when anticoagulants are in use.

The conquest of the thrombo-embolic aspects of the disease leads to a consideration of the other major causes of death—shock and congestive heart failure—in the hope that therapeutic measures as effective for their prevention and treatment may be forthcoming.

There is reason to believe that the occurrence of the severer grades of shock exerts a profound influence on the subsequent course of the illness. Severe and persistent shock, if survived, predisposes to death from congestive heart failure.

Prompt reversal of the shock mechanism should protect the healthy myocardium, reduce the death rate from this cause, and lessen the likelihood of congestive heart failure. The place of pressor drugs, intravenous and intra-arterial transfusions, and rapid digitalization in the treatment of shock is discussed. The early adoption of routine measures to prevent the development of congestive heart failure is also considered.

Anticoagulants have revealed our therapeutic shortcomings so far as these complications are concerned, but further advances in treatment can be anticipated as our understanding of the mechanism of cardiogenic shock improves.

In the conduct of these investigations I am most grateful for the co-operation of my colleagues, Dr. W. A. Alexander, Professor Stanley Davidson, Professor D. M. Dunlop, and Dr. W. D. D. Small. Dr. John A. Tulloch has been my constant collaborator.

REFERENCES

Barnett, A. J., Blackett, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 151.
Bedford, D. E. (1939). *Lancet*, **1**, 1303.
Berman, E. F., and Akman, L. C. (1952). *Amer. Heart J.*, **43**, 264.
Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M. (1941). *Arch. intern. Med.*, **68**, 181.
Boyer, N. H. (1944). *New. Engl. J. Med.*, **230**, 226.
Brams, W. A. (1948). *Treatment of Heart Disease*, p. 82. Philadelphia and London.
Brofman, B. L., Hellerstein, H. K., and Caskey, W. H. (1950). *J. Lab. clin. Med.*, **36**, 802.
Corday, E., Bergman, H. C., Schwartz, L. L., Spritzler, R. J., and Prinzmetal, M. (1949). *Amer. Heart J.*, **37**, 560.
Epstein, F. H., and Reiman, A. S. (1949). *New Engl. J. Med.*, **241**, 889.
Focht, F. S., and Hanson, H. T. (1948). *Amer. J. Med.*, **4**, 787.
Goldenberg, M., Apgar, V., Deterling, R., and Pines, K. L. (1949). *J. Amer. med. Ass.*, **140**, 776.
Hellerstein, H. K., and Brofman, B. L. (1951). *Mod. Conc. Cardiovas. Dis.*, **20**, 8.
Mallory, T. B. (1949-50). *J. Mt Sinai Hosp.*, **16**, 137.
Master, A. M. (1947). *Amer. J. Med.*, **2**, 501.
—— Dack, S., Field, L. E., and Horn, H. (1949). *J. Amer. med. Ass.*, **141**, 887.
Melcher, G. W., and Walcott, W. W. (1951). *Amer. J. Phys.*, **164**, 832.
Mintz, S. S., and Katz, L. N. (1947). *Arch. intern. Med.*, **80**, 205.
Page, I. H. (1949). *Amer. Heart J.*, **38**, 161.
Papp, C. (1952). *Brit. Heart J.*, **14**, 250.
Rinzler, S. H. (1951). *Cardiac Pain*, p. 29. Springfield.
Sampson, J. J., and Singer, I. M. (1949). *Amer. Heart J.*, **38**, 54.
Tulloch, J. A., and Gilchrist, A. R. (1950). *British Medical Journal*, **2**, 965.
—— —— (1951). *Amer. Heart J.*, **42**, 864.
Wright, I. S. (1952). *Circulation*, **5**, 161.
—— Marple, C. D., and Beck, D. F. (1948). *Amer. Heart J.*, **36**, 801.

TUBERCULOUS MENINGITIS

SOME ASPECTS OF ITS TREATMENT*

BY

A. R. SOMNER, M.D.

(From the Department of Tuberculosis and Diseases of the Respiratory System, University of Edinburgh, and Southfield Sanatorium, Edinburgh)

Large numbers of cases of tuberculous meningitis have now been treated in many countries and the results reported in full in the literature. This paper deals only with some aspects which have seemed important during treatment at this centre. During the period October, 1948, to May, 1951, 26 cases of tuberculous meningitis, admitted without selection, were started on treatment at Southfield Sanatorium. The youngest patient was aged 1 year and the oldest 27 years. Miliary tuberculosis was present in addition in 10 of the cases. In January, 1952, 14 (54%) of the patients were alive, with a minimum observation period of nine months and a maximum of 35 months since the beginning of treatment. Twelve of the 14 survivors have completed treatment and made a good recovery. The period of observation since finishing treatment is over twelve months in 10 of these 12 cases. The two cases remaining under treatment have been observed for twenty-eight and nine months respectively. In both a successful outcome is now confidently expected.

*Based on part of a thesis accepted by the University of Edinburgh for the degree of M.D.

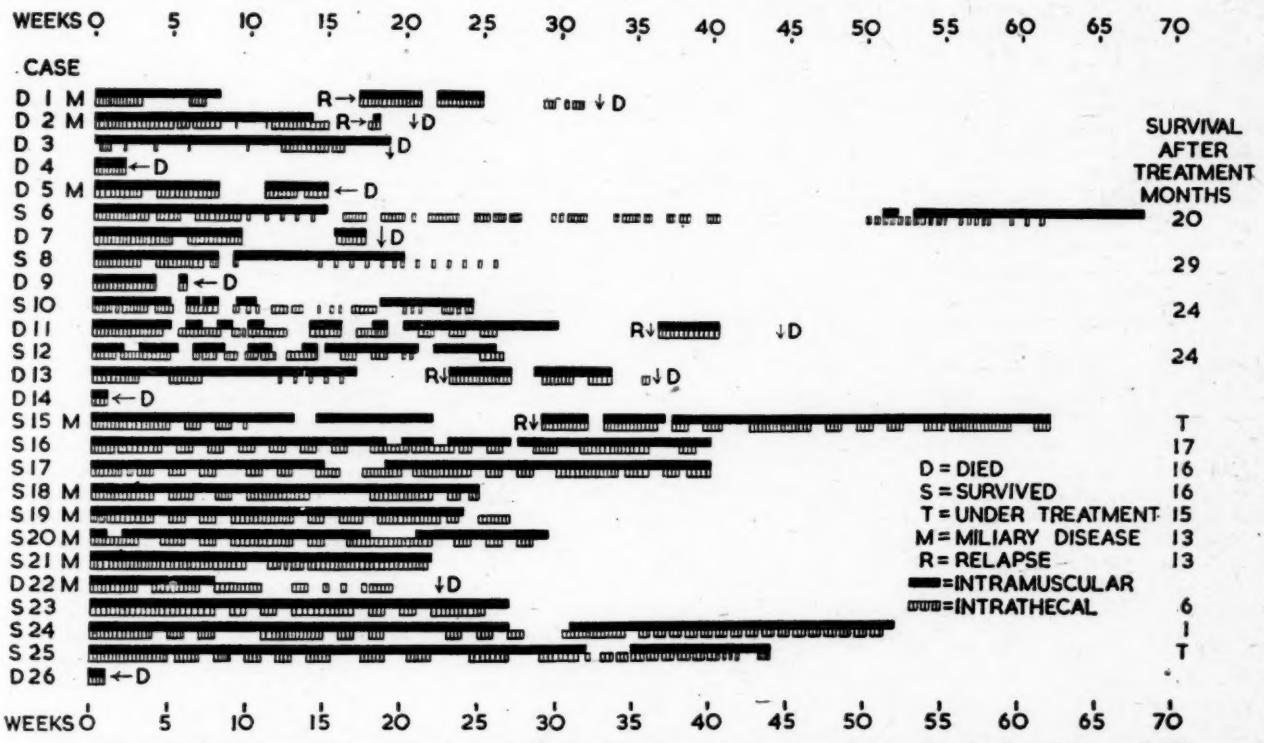
Treatment

When streptomycin was first used in this centre for treating meningitis a large percentage of cases relapsed a few weeks after receiving an initial course of two to four months' continuous systemic streptomycin. In spite of the resumption of treatment most of these patients died. The results were better when treatment was resumed within two to three weeks of the initial period of two to four months' therapy, so long as the patient had shown no evidence of deterioration in the interval. In view of the frequency of relapse with brief courses of treatment, it was planned to give a continuous intramuscular course for six months, and this plan affected the cases in the second half of this series (see Chart). The daily dose for an adult was 1 g. and for children 0.5 to 1 g. according to age. Of eight patients receiving an initial six months' period of treatment (combined with intrathecal injections on approximately 75% of the days), none has relapsed or died. Of the 12 who have given on 75% of the days on which intramuscular streptomycin was given. This percentage corresponds exactly to that recommended by the Ministry of Health (1950) in a survey of the treatment of over 350 cases of tuberculous meningitis. There were no subsequent deaths of patients who received 144 intrathecal injections.

Deafness

Deafness has been the most serious toxic manifestation of streptomycin encountered. Eight of the surviving cases received dihydrostreptomycin sulphate, both intramuscularly and intrathecally, during treatment, and all but one have shown impairment of hearing. Three cases were treated entirely with dihydrostreptomycin, and all have become totally deaf. The other four cases were treated partly with dihydrostreptomycin and partly with the streptomycin calcium chloride complex; one patient is totally deaf and three show varying degrees of deafness. In a previous communication (Somner, 1951) I reported that of the six surviving patients who had received either streptomycin sulphate or calcium chloride complex none showed any auditory impairment. Since then, however, one of these patients has complained of slight deafness in one ear (October, 1951); but this has not increased, as in the other cases, in spite of continuing treatment for a further four months. Sometimes dihydrostreptomycin deafness appeared slowly during the course of treatment and was progressive even after the cessation of treatment; at other times the onset of deafness was delayed for a few weeks after all treatment had been discontinued. In no case has any improvement occurred. Though it is perhaps difficult completely to exclude the possibility that the deafness was due to the disease, the difference in incidence with the two forms of streptomycin, and the onset of deafness at a time when other symptoms were absent or improving, strongly suggest that dihydrostreptomycin was responsible.

Biagi (1951) also stresses the danger to hearing from the use of dihydrostreptomycin in tuberculous meningitis. That the deafness is not dependent upon the intrathecal use of the drug was shown by Allison, Volk, and Vitagliano (1949),



An analysis of the duration of intramuscular and intrathecal streptomycin treatment in 26 cases of tuberculous meningitis.

completed treatment, the average total duration of intramuscular streptomycin was 10 days over the six months. The Chart shows that the minimum duration was 14 weeks (Case 10) and the maximum 49 weeks (Case 24). Relapse occurred in 5 out of 10 patients whose treatment was stopped before the end of six months, and only one responded when it was resumed. In only one of the dead did the total duration of treatment—that is, initial period plus subsequent courses of treatment—exceed that of the average of all the survivors. For these reasons all cases now receive a minimum of six months' streptomycin treatment.

Streptomycin was given intrathecally in all cases. The dose was 50 to 100 mg. The plan was to give an interrupted course of 42 injections every nine weeks. The injections were given continuously for four weeks, followed by seven days' rest, and during alternate weeks for the next four weeks. As each case was assessed independently it was not always possible to adhere to this plan. If it was followed throughout the average six months' course the number of injections would be about 120 in each case. The average number of intrathecal injections the survivors received was 144. This means that intrathecal therapy was

Shane and Laurie (1950), and O'Connor, Christie, and Howlett (1951), who carried out controlled investigations on cases suffering from pulmonary tuberculosis alone. The incidence of deafness with dihydrostreptomycin was in striking contrast to that produced by streptomycin. In view of this risk, and in particular because of the possibility of a delayed onset of deafness even after the drug is stopped, its use in the prolonged treatment of meningitis is no longer justifiable. At present streptomycin itself seems the drug of choice.

Sugar Content of Cerebrospinal Fluid

A normal sugar is regarded as 50 mg. per 100 ml. or over in this paper. Other workers have regarded 45 mg. as a normal figure, but experience with the cases under discussion has shown this figure to be too low, as recrudescence of the disease is still apt to occur if treatment is discontinued at this stage.

The sugar estimation has been found to be the most valuable single factor in the early diagnosis of cases of tuberculous meningitis not complicated by miliary tuberculosis. With cases of miliary tuberculosis it may be possible to recognize a subsequent development of meningitis by the slight pleocytosis of the cerebrospinal fluid (C.S.F.) found on routine lumbar puncture before an appreciable fall in the sugar level occurs. The assessment of progress of the meningitis is also accurately portrayed by the sugar estimation. All the cases which presented with features of tuberculous meningitis, uncomplicated by miliary tuberculosis, gave a sugar value below 50 mg. per 100 ml. The cases that presented with miliary tuberculosis and subsequently developed meningitis were naturally diagnosed at an earlier stage and generally presented slightly higher sugar levels. In two instances of the latter, levels of 50 mg. per 100 ml. were obtained at the time of diagnosis.

The sugar level falls with progressive disease and rises as the disease process undergoes resolution. It is a most reliable guide and not subject to the fluctuations shown by the other constituents of the C.S.F. It has been found that the morbid state of the disease is quite accurately portrayed by the sugar levels; which is fortunate, for it cannot be accurately assessed from the patient's clinical condition. The sugar estimation at the time of diagnosis is usually in accord with the clinical severity of the disease, but once streptomycin therapy is started the clinical improvement which occurs often bears little relation to the C.S.F. findings. A striking fact seen in many of these cases is the remarkable clinical improvement which occurs under treatment, yet the persistent failure of the sugar to rise is a sober reminder that all is far from well. The lesson has been forcibly learned that a patient without symptoms and without clinical evidence of meningitis but with a C.S.F. sugar below 50 mg. per 100 ml. is in danger of recrudescence of the disease in the near future if streptomycin treatment is interrupted or discontinued.

It is now the practice to continue streptomycin treatment in all patients until the sugar level is 50 mg. per 100 ml. or over, no matter how favourable all other aspects of their condition appear. In the patient making a normal response to treatment the clinical improvement moves ahead of the improvement in the sugar values of the C.S.F. The Table shows that, with the minor exceptions mentioned in the three cases treated in 1949–50, the sugar level had risen above 50 mg. per 100 ml. before treatment was discontinued, and it further shows the prolonged period necessary before this occurs. Relapse has so far occurred in only one patient (Case 15) who had attained a sugar level about 50 mg. per 100 ml. The initial period of treatment in this patient, on retrospect, appears inadequate. If the sugar remains stationary at a low level month after month the outlook is unfavourable, but persistent treatment may lead to eventual success. Any interruption of treatment usually leads to failure. A falling sugar level after the institution of energetic treatment is always a bad prognostic sign.

An Analysis of the Time Required for the C.S.F. Sugar Level to Rise Above 50 mg. per 100 ml. in Cases of Tuberculous Meningitis Successfully Treated

Case No.	Months of Streptomycin Treatment	Month After Admission at which C.S.F. Sugar Level of 50 mg./100 ml. Reached	Remarks
6	14	16th	Treatment stopped at 49 mg./100ml. 2 months before C.S.F. sugar over 50 mg./100 ml.
8	8	5th	
10	5	7th	Treatment stopped at 46 mg./100 ml., 2 months before C.S.F. sugar over 50 mg./100 ml.
12	6	7th	Treatment stopped at 48 mg./100 ml. 1 month before C.S.F. sugar over 50 mg./100 ml.
15	23	27th	Still under treatment
16	10	10th	Treatment completed
17	10	10th	
18	6	6th	
19	8	7th	
20	6	5th	
21	5	4th	
23	7	7th	
24	12	10th	
25	9	—	Still under treatment. Sugar 48 mg./100 ml.

Chloride Content of C.S.F.

The constancy and reliability of the sugar estimation now being realized, less significance is attached to the chloride content of the C.S.F. A normal chloride is regarded as 720 mg. per 100 ml. or over in this paper. From the diagnostic standpoint, all cases presenting features of meningitis on admission, with one exception, had a chloride value below 700 mg. per 100 ml. In 5 of the 26 cases meningitis was diagnosed when the level was above this, and these developed meningitis while under treatment for miliary tuberculosis. Though less reliable than the sugar value and tending to fluctuate for little apparent reason, the chloride content of the C.S.F. has nevertheless reflected the changes in the clinical state of the patient and in general has followed the same course as the sugar. The chloride value usually reaches normality before the sugar content does, but thereafter the former shows slight fluctuations between normality and abnormality for a short time, not seen with the sugar value. In all 26 cases in this series the sugar values were closely paralleled by the rising and falling chloride content, and in all the survivors the chloride content was above 720 mg. per 100 ml. at the time treatment was stopped.

White-cell and Protein Content of C.S.F.

These two constituents of the C.S.F. are considered together because each appears to vary in the same direction during the course of treatment of meningitis. Smith and Vollum (1950) have published several interesting observations on the relationship of streptomycin to the C.S.F. changes in tuberculous meningitis. They point out that the total cell count in the treated case was usually above the range seen in the untreated case. During the first week or two of intrathecal streptomycin the cell count would rise and show frequent fluctuations, and at the peaks about 80% of the cells were polymorphonuclear leucocytes. This phenomenon continued during the acute stage, but as improvement occurred, and while intrathecal streptomycin continued to be given, the cell fluctuations and their total numbers fell steadily, while the polymorph was gradually replaced by the lymphocyte. Elevation and fluctuation of the protein level frequently occurred during treatment, corresponding approximately to the fluctuations of the cellular element, and as the patient improved the protein level became reduced in spite of the continuation of treatment. The C.S.F. picture of the present cases conformed closely to this general pattern.

In support of the view that the high and fluctuating cell and protein contents are an indication of the activity of the

meningitis, Smith and Vollum (1950) further point out that it is not possible to reproduce these phenomena when subsequent intrathecal streptomycin is given if active meningitis has subsided. The phenomena are thus regarded as a specific reaction of tuberculous meningitis influenced by streptomycin, and may be due to the liberation of bacterial breakdown products—for example, tuberculin—into the subarachnoid space of the sensitized patient.

In the assessment of progress under treatment the protein and cell contents, though an additional aid, have not been found comparable to the sugar value in accuracy and constancy. As the disease process comes under control a gradual fall occurs with the former, but in all the cases apparently cured it has been noted that a normal cell count (5 cells per c.mm.) and protein content (40 mg. per 100 ml.) are never obtained so long as intrathecal streptomycin continues to be given. They are the last of the C.S.F. constituents to return to normal, usually long after the sugar and chloride have done so. The time taken for the cells, and particularly the protein content, to return to normal after the cessation of treatment has been found to vary between 2 and 20 months in the survivors in this series.

Spinal Block and Cisternal Streptomycin Injections

Spinal block occurred, sometimes more than once in the same patient, in 11 of the 26 cases under discussion. Partial block was much commoner than complete block.

The common cause of spinal obstruction is the presence of gelatinous exudate within the narrow spinal subarachnoid space. The duration of this complication is variable and unpredictable. In fact, it is surprising how quickly evidence of partial block subsides, and it does not always seem reasonable to suppose that canalization through the exudate could have taken place in so short a time. The answer to this may lie, as Choremis *et al.* (1951) have pointed out, in the ability of streptomycin itself to precipitate an already incipient block. Streptomycin injected into the normal theca causes an immediate pleocytosis and outpouring of protein into the C.S.F. (Choremis *et al.*, 1948 ; Cathie, 1948). As a result of this congestion of the meninges and of the tuberculous exudate already there from a downward extension of the disease, it is reasonable to suppose that spinal obstruction can be readily produced. Several cases in this series have shown interesting examples of this. Partial spinal obstruction was diagnosed and intrathecal streptomycin was administered by the cisternal route. In some cases, when a lumbar puncture was repeated after a matter of only a few days, it was surprising to find that all evidence of spinal block had disappeared. This has occurred on so many occasions that there can be little doubt that the administration of intrathecal streptomycin can precipitate the development of spinal block and that a few days' rest will often lead to its resolution. When resumed again the intrathecal dose is reduced from 100 to 50 mg. for adults and from 50 to 25 mg. for children.

In other cases the partial spinal obstruction persisted and resort was made to the cisternal injection of streptomycin. The cisternal route was never used as an alternative to the lumbar route simply to rest this area or where lumbar puncture was difficult, for it has been found that reactions by the cisternal route are not only annoying to the patient but are also potentially dangerous if repeated too often.

The cisternal punctures were carried out, apart from the initial one, without the use of a local analgesic, and it was surprising how little was the discomfort caused to the patient. While the streptomycin was being injected patients complained of various symptoms. The commonest were a sensation of "burning pain" in the region of the head, face, and neck or a bursting sensation in the ears ; in some, vomiting occurred immediately the injection was completed, and this tendency was reduced by withdrawal of 5 ml. of C.S.F. before the injection was given. The patient often felt drowsy for most of the remainder of the day. The most consistent feature following cisternal streptomycin has been the acute vestibular disturbance which occurred about half an hour after nearly every injection: a coarse nystagmus developed—often so coarse that lateral movement of the eyes was not required to elicit it ; sometimes it caused jerking movements of the upper eyelids. The patient very commonly complained of double vision, which prevented reading. Both these features persisted for the greater part of the day, though gradually diminishing, and were either minimal or absent at the time of the injection next day, which again led to their exacerbation.

One important drawback to repeated cisternal streptomycin injections has been the occurrence of haemorrhage into the subarachnoid space. The largest number of cisternal injections given to any patient in this series was 46 within a period of 12 weeks. Haemorrhage occurred on four different occasions and caused her so much distress that this route had to be finally abandoned in favour of the lumbar route, which had not yet opened up completely. The symptoms of these episodes were severe headache and backache and root pains radiating around the trunk. A cisternal puncture on the day following the symptoms of haemorrhage confirmed that the C.S.F. was heavily blood-stained. The symptoms cleared up in about five days, and during this period intrathecal streptomycin was omitted. It seems very undesirable that such haemorrhages should occur, as the blood must aggravate the partial obstruction caused by the tuberculous exudate in the narrow spinal subarachnoid space.

Choroidal Tubercles

Cases of miliary tuberculosis and tuberculous meningitis may show tubercles of the choroid. The prolongation of life which has resulted from the use of streptomycin has provided the opportunity of studying the natural history of these choroidal lesions.

Emery and Lorber (1950) drew attention to the fact that in a series of 52 children who died of miliary tuberculosis, histologically proved, in only one-third was the diagnosis made by *x*-ray examination during life. On the other hand, choroidal tubercles were seen in half the cases during life, and in general led to a diagnosis of miliary tuberculosis more often than did radiological examination. Illingworth and Wright (1948) fully reviewed the subject, and found choroidal tubercles in 25 (60%) of their 42 cases of miliary tuberculosis. In the present series of 26 cases of tuberculous meningitis 10 suffered from miliary tuberculosis and choroidal tubercles were found in 7 of these (70%). None were found in the 16 cases of meningitis in which there was no miliary disease. (Since this series was investigated a single choroidal tubercle has been found in the fundus of a case of meningitis without radiological evidence of miliary disease.) Though the choroidal tubercles were usually found at the time of the first or second examination, this was not always the case.

In a girl aged 7 years two tubercles were present in the left fundus at the time miliary tuberculosis was diagnosed. Meningitis subsequently developed, but it was not until nine months later that a third tubercle was found. Fourteen months after the beginning of her illness a further three tubercles were found, quite unexpectedly, and one month later again a seventh one, all in the original fundus. It seems probable that these lesions had been previously missed. Each succeeding tubercle found was further and further away from the disk, and thus was more easily overlooked on routine examination, which had been carried out at least once a fortnight throughout the course of her illness. In fact, the seventh tubercle to be discovered was only just visible with the pupil fully dilated by homatropine. The tubercles that were found last were obviously not the result of fresh dissemination, because all contained some degree of pigmentation.

In the earliest stages the choroidal tubercles appeared as circular pale-yellow areas with an indefinite edge merging into the red background of the choroid. The larger ones

appeared raised above the surface. The largest number found in one fundus was 13. In three cases tubercles were present in one eye only, and in the other four cases in both fundi. They were found to be most numerous close to the disk, and were about one-fifth the diameter of the optic disk. During the treatment of these seven cases only slight changes have been observed in the choroidal tubercles over a period of many months—the longest period has been 27 months. No tubercles have been seen to disappear completely. Most remain unchanged for about three months. The first change noticed was that the tubercle became a deeper yellow and the outline became more distinct as the retinal oedema subsided. Fine dots of black pigmentation then appeared in and around the tubercle. Later still this pigmentation increased in, and particularly around, the lesion.

Illingworth and Wright (1948) regard the healed tubercle as one which shows a parchment-white scar, with a well-defined sharp edge and heavy black pigmentation. None of the cases in this series, including that observed for 27 months, showed such a picture,* but instead one in which the individual lesions became a deeper yellow, sometimes even orange-yellow, so that the contrast between the colour of the tubercle and that of the normal choroid became less and less distinctive. The edge of each lesion became sharp in outline, though sometimes it was of an irregular shape, and dots of pigmentation occurred within and around the tubercle. This final phase of development has seldom been seen to occur in less than six months. Of the seven patients with tubercles in the fundi, five have survived, and the minimum observation period has been 16 months. In none have the choroidal tubercles developed beyond the "intermediate stage" described by Illingworth and Wright, who state that the final stage of healing may be reached in 12 to 14 weeks. It is of course not possible to say that the choroidal lesions in the present series are definitely healed, but when assessed in conjunction with the state of the miliary and meningeal disease it may be surmised that the phase of arrest or healing has been reached. Lastly, Illingworth and Wright noted that the survival rate was more encouraging in those who showed the tubercles to be in the "final or healed stage" than when in the "intermediate stage" which they describe. As all the cases observed by me fall into this "intermediate stage," a survival rate of five out of seven cases cannot be regarded as unsatisfactory.

Summary

The streptomycin treatment of 26 cases of tuberculous meningitis is described. There are 14 survivors, 10 of whom have been followed up for over twelve months since stopping treatment. The average duration of the systemic administration of the drug to the survivors was a little over six months, and intrathecal injections were given to each on an average of 75% of the days on which intramuscular streptomycin was given. None of those who died received treatment of greater duration. The serious incidence of deafness occurring with the use of dihydrostreptomycin is reported.

The sugar content of the cerebrospinal fluid was found to be the most valuable index of assessment of progress, and it is suggested that treatment should never be discontinued so long as this level is below 50 mg. per 100 ml. The significance of the protein and cell contents is discussed. It is pointed out that neither of them may return to normal for many months after treatment has ceased.

Intrathecal streptomycin was found to be an additional factor in the development of spinal block in some cases. Symptoms and signs resulting from the alternative use of the cisternal route are described.

A description is given of choroidal tubercles, with special reference to the appearance of the healed lesion as seen in 7 out of 10 cases of miliary tuberculosis.

*A case of miliary tuberculosis with meningitis, admitted too late to be included in the series and still under treatment, does show this picture very clearly. Two tubercles are pure white with a dense central and peripheral zone of pigmentation. It is interesting to find in addition in this patient three tubercles in the early stage of development entirely devoid of pigmentation.

For advice on specialized points acknowledgment is gladly made to Professor Charles Cameron, to Dr. J. K. Slater, visiting neurologist, and to Dr. John Macaskill, visiting ophthalmologist. I also wish to thank Professor J. W. Crofton for his kindly criticism of this paper.

REFERENCES

Allison, S. T., Volk, R., and Vitagliano, G. R. (1949). *New Engl. J. Med.*, **241**, 52.
Biagi, R. W. (1951). *British Medical Journal*, **2**, 651.
Cathie, I. A. B. (1948). *Post-grad. med. J.*, **24**, 351.
Choremis, K., Constantinides, V., Zervos, N., and Pantazis, S. (1948). *Lancet*, **2**, 595.
—— Zervos, N., Pantazis, S., Priftis, N., and Papatheodorou, N. (1951). *Acta tuberc. scand.*, **25**, 8.
Emery, J. L., and Lorber, J. (1950). *British Medical Journal*, **2**, 702.
Illingworth, R. S., and Wright, T. (1948). Ibid., **2**, 365.
Ministry of Health (1950). *Tubercle*, **31**, 214.
O'Connor, J. B., Christie, F. J., and Howlett, K. S. (1951). *Amer. Rev. Tuberc.*, **63**, 312.
Shane, S. J., and Laurie, J. H. (1950). *Canad. med. Ass. J.*, **63**, 277.
Smith, H. V., and Vollum, R. L. (1950). *Lancet*, **2**, 275.
Somner, A. R. (1951). *British Medical Journal*, **2**, 970.

OBSERVATIONS ON THE LABORATORY DIAGNOSIS OF TUBERCULOUS MENINGITIS

BY

R. W. S. HARVEY, M.B., Ch.B., B.Sc., Dipl.Bact.

(From the Public Health Laboratory, Cardiff)

Rapid laboratory diagnosis of tuberculous meningitis is sometimes thought to be a matter of difficulty, and since the introduction of streptomycin therapy emphasis has shifted from late confirmatory to rapid presumptive methods. The former include cultural and animal inoculation tests, the latter simple biochemical tests, cell counts, and microscopical examination of clot or centrifuged deposit of tubercle bacilli.

This report summarizes the experience gained from the examination of cerebrospinal fluids from 150 cases of tuberculous meningitis admitted to hospital for treatment with streptomycin. The report relates exclusively (except where otherwise stated) to the examination of the first specimen received from each patient—that is, to the specimen submitted to establish the diagnosis. The tests were carried out in a routine laboratory and not in a special department. The tests were often made on as little as 3 ml. of fluid, and in the early stages of the investigations the available fluid was divided into two equal parts so that accurate chemical tests could be made in another laboratory. With comparatively few exceptions, however, it was possible to make a rapid presumptive diagnosis of tuberculous meningitis which was confirmed by cultural and animal inoculation tests.

Technical Methods

The following tests were used: (1) Test for glucose (using Benedict's solution); (2) Pandy's test for globulin; (3) cell count; (4) microscopical examination for *Mycobacterium tuberculosis*; (5) culture; (6) animal inoculation.

1. *Benedict's Test for Glucose.*—Equal volumes of cerebrospinal fluid (C.S.F.) and Benedict's solution (qualitative) were mixed in a small tube, which was then immersed in a bath of boiling water for five minutes. A normal C.S.F. and any abnormal but clear fluid not tuberculous produce, with very rare exceptions, considerable reduction of the Benedict's solution. A tuberculous fluid, on the other hand, generally produces no apparent reduction, or at the most only a trace; exceptions to this finding were, in our experience, rare. This examination was found to be the most useful of all the simple tests because it possessed a certain degree of specificity as a diagnostic test. On occasion it was necessary to test for sugar, using minute volumes of fluid. As little as three drops of C.S.F. were placed in a Durham tube and the same volume of Benedict's solution was added with care so that the amount of reduction at the interface could be read as a "ring" test.

2. *Pandy's Test for Globulin.*—Qualitative tests for globulin in the C.S.F. have been criticized for lack of specificity, and quantitative methods of protein estimation for their inaccuracy. Despite the defects of tests for protein, the globulin test is of value in the diagnosis of tuberculous meningitis. There is some correlation between the cell count and the turbidity obtained by the addition of Pandy's reagent. On the whole it was found that a moderate turbidity obtained on the addition of Pandy's reagent to a C.S.F. was useful supporting evidence when the other preliminary examinations favoured the diagnosis of tuberculous meningitis. The smallest convenient volume of C.S.F. was placed in a tube, and to it was added four times its volume of Pandy's reagent. The resulting turbidity, if such occurred, was roughly recorded as +, ++, or +++. Obviously this test had not in itself the same diagnostic value as the test for glucose.

3. *Cell Count.*—A Fuchs–Rosenthal chamber was used not only to count the white cells but also to determine whether or not there were any red cells present. The proportion of polymorphs and lymphocytes was approximately assessed during the examination of the deposit stained by the Ziehl–Neelsen method. As the proportion depends partly upon the stage of the illness, it is advisable to have some knowledge of the date of onset of the illness.

4. *Examination of the Centrifuged Deposit for Tubercle Bacilli.*—If a clot was present a film was made and stained by the Ziehl–Neelsen method, but the microscopical examination of a centrifuged deposit in the following way was preferred:

Miniature centrifuge tubes were made by sealing off Pasteur pipettes about ½ in. (1 cm.) below the barrel, thus making a tube of about 1 ml. capacity with a conical lower end. All that remained of the fluid after completing the previous tests was distributed into such tubes and centrifuged at 3,000 r.p.m. for 20–30 minutes. This produced a minute but nevertheless intense concentration of deposit in the apex of the cone. The supernatant fluid was removed by a Pasteur pipette and discarded unless it was required for some other purpose. The end of this pipette was then drawn out in the pilot flame of a Bunsen burner into a fine capillary tube, which was cut squarely across, leaving approximately ½ in. (1.3 cm.) of capillary at the end of the pipette. For this purpose a small piece of carborundum chip mounted on a pencil-like holder with sealing-wax was found most suitable. The capillary was then introduced into the Pasteur pipette in which the fluid had been centrifuged, and the sediment was withdrawn and deposited in the form of a series of disconnected drops on a microscope slide. The average diameter of each drop was about 2 mm. The drops were stained and examined for tubercle bacilli. Each stained drop covered approximately 100 microscopical fields, and four to five drops could be made from the deposit from 1 ml. of C.S.F.: 1 ml. would thus yield 400–500 microscopical fields available for search if necessary, the whole broken up into units of approximately 100. To search these small areas was much less fatiguing than prolonged examination of a large smear.

For microscopical examination these films were preferred to preparations made from a clot, though tubercle bacilli were occasionally found in the clot when none were found in the films of the centrifuged deposit. When red blood cells were present in the deposit the smear was treated with a drop of water before staining. The water used for this purpose should be above suspicion as a source of saprophytic mycobacteria. The results of the microscopical examinations are given below together with a statement about the time spent at the microscope to find tubercle bacilli.

5. *Culture.*—Löwenstein–Jensen and Dorset egg slopes were inoculated with the centrifuged deposits as described above, the entire deposit from one tube (representing 1 ml. of C.S.F.) being placed on the slope; the number of tubes inoculated thus depended upon the volume of C.S.F. submitted. A mild treatment with acid was given to the deposit to reduce the risk of contamination of the cultures. The fine capillary end of the Pasteur pipette was filled with 4% sulphuric acid and the deposit was then sucked up. Without delay, and therefore without neutralization, the culture medium was inoculated and the cultures incubated for six to eight weeks.

6. *Guinea-pig Inoculation.*—A guinea-pig was inoculated with the deposit from 1 ml. of C.S.F. and killed after six weeks. A post-mortem examination was made and lesions were sought in the superficial and deep inguinal glands, lumbar glands, and spleen. Smears were made, preferably from the deep inguinal glands or sublumbar glands, and stained and examined for typical acid-fast bacilli. Cultures of the lesions were made when there was any doubt about the post-mortem findings. It will be noted that whereas only one guinea-pig was inoculated, and then only with the equivalent of 1 ml. of C.S.F., several cultures (depending upon the volume of fluid submitted) were made, so any comparison between the success of the two methods should perhaps take the quantitative differences into account.

Results

There were 150 cases in which the diagnosis was accepted clinically as tuberculous meningitis. All had been admitted to a special centre for diagnosis and treatment with streptomycin, and it was of value to the clinician in charge of the patient to know quickly if there was enough laboratory evidence to support the clinical evidence for him to begin treatment at once. If the preliminary tests did not suggest the diagnosis of tuberculous meningitis the patient was not treated.

As the patients had already been admitted to hospital and were under observation for some time whether or not the diagnosis of tuberculous meningitis was made, the true diagnosis would have become apparent if any cases of tuberculous meningitis had escaped detection by the laboratory.

Of the 150 cases accepted as suffering from tuberculous meningitis an unchallengeable diagnosis was made in 131 (87%) by the demonstration of the tubercle bacillus in culture or in the inoculated guinea-pig. Of the remaining 19, acid-fast bacilli were seen in film in 7, and histological or bacteriological evidence was obtained post mortem in 3, but in 9 patients, all still alive, though clinical evidence was supported by biochemical and cytological examinations, tubercle bacilli were not found in film, culture, or guinea-pig.

The diagnosis of tuberculous meningitis was thus confirmed beyond reasonable doubt by laboratory tests in 141 cases, but the full records included the examination of post-mortem material from patients and the results of the examination of many samples of fluids from each patient during treatment.

It seemed important, however, to decide upon the value to be attached to the various tests made on the initial sample of fluid submitted from each patient to establish the diagnosis. It is the results of these examinations which are presented here.

Sugar.—Of the simple tests there was no doubt of the value of the examination for sugar. In 144 of 150 cases

the initial sample of fluid submitted was clearly deficient in sugar. In only six cases did the sugar test fail to indicate the diagnosis. Moreover, during the period over which these examinations were made in a busy routine laboratory, on no occasion when a clear fluid was found deficient in sugar was the diagnosis proved not to be tuberculous meningitis. It appears that a greatly reduced sugar content in a clear fluid is strongly indicative of tuberculous meningitis; but the possibility of benign lymphocytic choriomeningitis would have to be borne in mind, as a reduced sugar content of the cerebrospinal fluid is sometimes found in this disease.

Microscopy.—The examination of stained films of the centrifuged deposits was preferred to the examination of a clot, though on occasion bacilli were found in the clot before they were found in the deposit. Tubercle bacilli were found in the stained film in 103 of the 150 initial specimens submitted (69% positive). If later specimens of fluid are taken into account the total rises to 111 (74%). In order to show that the microscopical examination was not unduly laborious a note was kept of the time spent in the search in 71 consecutive positives (Table I).

TABLE I.—*Time Taken to Demonstrate Tubercle Bacilli in Film (71 Specimens)*

Time in minutes:	<5	5–9	10–14	15–19	20–29	30–39	40 and Over
No. positive:	29	16	8	2	5	5	6

Culture and Guinea-pig Tests.—Of the 150 initial specimens, 103 yielded positive cultures (69%) and 100 (67%) were positive by animal inoculation tests. Thus the three tests—film, culture, and guinea-pig inoculation—were all more or less equally successful in demonstrating tuberculous infection (Table II). Before making too close a comparison, however, it should be remembered that the equivalent of only 1 ml. of fluid was injected into a guinea-pig, whereas all that remained after the other tests were done was centrifuged and cultured. In six cases no results were obtained by the guinea-pig inoculation test, owing to premature deaths of the animals or because insufficient fluid was submitted. If examinations of later specimens are taken into account 114 (76%) were positive on culture.

TABLE II.—*Results of Examination of Primary Diagnostic Specimen Compared with Results of Examination of All Specimens of a Case of Tuberculous Meningitis*

Method of Examination Giving Positive Result	No. of Positive Results when Primary Specimen Done is Considered	No. of Positive Results when All Specimens Submitted are Considered
Film	103 (69%)	111 (74%)
Culture	103 (69%)	114 (76%)
Guinea-pig	100 (67%)	Only primary specimen was tested by guinea-pig inoculation

Results of Various Methods

Table III shows in more detail the comparison of film, culture, and animal inoculation test in the 150 cases. In 19 instances the examination of the *initial* specimen did not reveal tubercle bacilli in film, culture, or guinea-pig. Seven of these cases were confirmed by examination of later specimens—one by direct microscopy only, two by microscopy and culture, and four by culture only. There were thus 12 cases in which tubercle bacilli could not be demonstrated at any time before or during treatment. Three of these patients died, and the diagnosis was confirmed at post-mortem examination. The remaining nine patients, all still alive, were diagnosed on clinical grounds, supported only by the results of biochemical and cytological examinations of the cerebrospinal fluid.

TABLE III.—*Comparison of Results of Different Methods of Demonstrating Tubercle Bacilli in 150 Cases of Tuberculous Meningitis*

Film	Culture	Guinea-pig	No.
+	+	+	68
+	+	−	12
+	−	−	6*
+	−	+	11
−	+	−	7
−	+	+	11
−	−	+	10
+	+	0	5
+	−	0	1
−	−	−	19

* One of these cases was confirmed by culture of a later specimen.
0 = No result entered, either because the guinea-pig died prematurely or because insufficient fluid was submitted for the test.

Discussion

The cases of tuberculous meningitis examined in this series were unselected. With a few exceptions they had been admitted to one hospital for treatment. Of the cases whose first pre-treatment specimen of C.S.F. was examined in this laboratory, none which were treated for tuberculous meningitis by the clinician have been excluded from this series, whether they were bacteriologically confirmed or not. When suspected cases were admitted to hospital and neither clinician nor bacteriologist was satisfied the case was not treated, but if true cases had been left untreated the correct diagnosis would surely have become manifest while the patient was still in hospital.

Of the immediate examinations made on the cerebrospinal fluid there was no doubt of the value of a qualitative test for glucose. The technique was as simple as that used by a clinician testing for sugar in urine, yet the test was exceedingly reliable. On only 6 occasions out of 150 did it fail to point to the diagnosis. This simple test had another great virtue. By its use it was possible to demonstrate in a few seconds whether or not tuberculous meningitis was the probable diagnosis, and this knowledge made the microscopist more patient in his search for tubercle bacilli.

Other tests, such as cell count and Pandy's test for globulin, though necessary and valuable, did not possess the same specificity as the test for glucose.

In examining for the presence of tubercle bacilli by microscopy, films made from a centrifuged deposit were preferred to the examination of the clot, but it was essential to use a centrifuge tube with a conical and not a round bottom to obtain a dense although minute deposit.

The results of microscopy, culture, and guinea-pig inoculation were all positive to the same degree (69%, 69%, and 67% respectively). Strict comparison of these figures is not fair, as only 1 ml. of fluid was injected into a guinea-pig, whereas the deposit from several millilitres was usually inoculated on culture media. The volumes of fluid submitted for examination were very variable and often as little as 3 ml.

In 79 instances both culture and guinea-pig test were positive; in 19 the culture was positive and the guinea-pig test negative; in 21 the culture was negative and the guinea-pig test positive; and in 25 both tests were negative.

Unfortunately it was not possible to inoculate the strains into rabbits to establish beyond doubt how many of the strains were human or bovine tubercle bacilli, but inspection of the cultures indicated that only two or three were bovine. Although bovine strains are admittedly more difficult to isolate in culture, it was concluded that such strains had probably not been missed in this way because of the randomness of success or failure of culture as compared with the guinea-pig test.

Summary

Samples of cerebrospinal fluid were examined from 150 cases of tuberculous meningitis. Tubercle bacilli were found in film in 103 (69%), in culture in 103 (69%),

and by guinea-pig inoculation in 100 (67%). These results relate only to the initial specimens received and do not include additional positives found after treatment was begun.

A simple test for glucose showed a significantly low concentration in 144 specimens out of 150.

The cases examined were quite unselected.

The methods used were simple and easily carried out in a busy routine laboratory.

I wish to record my appreciation to Dr. G.-S. Wilson and Dr. S. Thompson, of the Public Health Laboratory Service, for much help in the setting out and arrangement of this paper, and to Mr. J. A. Smith and Mr. T. H. Price for their painstaking technical assistance and suggestions during the course of the work.

HYPERSENSITIVITY, STRESS, AND TOXICITY*

BY

T. W. LEES, M.B., Ch.B.

(From the Department of Surgery, University of Edinburgh)

In 1947 the importance of the adrenal cortex in the general reaction to disease and injury was being emphasized. It had been suggested that many diseases formerly thought to be inflammatory or infective in character were in fact the result of endocrine imbalance or insufficiency, the sequel to non-specific "stress."

It was therefore decided at that time to investigate the influence of the thyroid on the type of hypersensitivity which can be produced in the rabbit by repeated injections of foreign protein. It was argued that removal of the thyroid gland or an excess of thyroid hormone would cause stress and increase the liability to allergic reactions by upsetting the hormonal balance within the body and by impairing the re-equilibrating function of the adrenal cortex.

Although the skin was not the organ in which the primary interest lay, skin sensitivity was employed as the most convenient way of assessing the general state of hypersensitivity of the animal.

Method

Stock rabbits about 3 months old, with white skins, were weighed once a week for several weeks. When shown to be healthy and gaining weight a group of three animals of about the same weight and of the same sex were selected. One of these rabbits was chosen at random and subjected to thyroidectomy. The operation was considered successful if at the end of three months the animal had become lethargic and unduly sensitive to cold, and if its food intake was appreciably less than the control. Eight weeks after thyroidectomy in the first animal a second animal was fed thyroid extract *B.P.* in a dose of 3 gr. (0.2 g.) three times weekly. Such dosage produced considerable loss of weight and, if continued, caused death. When the animal's weight had been reduced to two-thirds of the initial level the dosage was adjusted to maintain it at this lower level.

At the beginning of the fifth month all three animals were made hypersensitive to horse serum by subcutaneous injections of this protein in 1- or 2-ml. doses. Thereafter "boosting" doses were given at intervals to all three animals to maintain the control animal at a moderate level of hypersensitivity. All the animals in any one group received equal doses simultaneously. There were seven groups of animals. The thyroid-fed animal in group V died before any skin tests were made—it is suspected from overdosage. An extra thyroidectomized animal was included in group IV and it received the same injections as the others in the group.

The skin testing was carried out without any fixed time relationship to the subcutaneous injections, except that no test was made less than five days after a subcutaneous injection. The test consisted in injecting intradermally 0.1 ml. of horse serum into the centre of an area of skin cleared of hair.

Measurement of the area of reaction indicated by (*a*) oedema, (*b*) haemorrhage, (*c*) necrosis, and (*d*) ulceration was made 24, 72, and 120 hours after the injection, and usually 48 hours after as well. The area of necrosis or haemorrhage was roughly circular or broadly elliptical. The longest axis of the ellipse was measured to the nearest millimetre, as was the broadest diameter at right angles to this. The area of the ellipse was obtained. If the area of haemorrhage or necrosis was minimal or doubtfully present it was assumed to be 4 mm. in diameter. In Table I the largest area of haemorrhage or necrosis recorded at any time after each intradermal injection is listed.

TABLE I.—*Areas of Reaction (in mm.²) Following Intracutaneous Injection of 0.1 ml. Horse Serum Into Rabbits Sensitized to this Protein*

Group	Treatment	Area of Reaction		Group	Treatment	Area of Reaction		Group	Treatment	Area of Reaction	
		Haem.	Necr.			Haem.	Necr.			Haem.	Necr.
I	0	116	141	IV	0	484	352	V	0	28	28
	−	38	25		−	57	28		−	236	283
	+	550	63		+	412	352		0	864	393
II	0	57	13		0	490	490		−	864	591
	−	?13	?13		−	38	63		0	352	273
	+	267	75		−	13	13		−	113	?13
	0	101	101		+	355	471	VI	0	352	352
	−	?13	?13		0	471	471		−	35	13
	+	116	19		−	57	25		+	591	?314
	0	47	25		−	28	13		0	597	597
	−	19	?13		+	826	424		−	141	94
	+	110	94		0	412	358		+	?346	?13
III	0	223	119		−	214	113		0	185	94
	−	346	188		−	28	13		−	267	88
	+	368	129		+	848	848		+	?13	?13
	0	207	138		0	295	198	VII	0	132	38
	−	163	129		−	38	38		−	44	13
	+	163	31		−	13	13		+	13	13
	0	126	126		+	?1,414	?13		0	440	402
	−	110	110		0	204	204		−	19	13
	+	358	251		−	110	107		+	19	13
	0	57	50		−	63	19		0	352	330
	−	28	16		+	286	283		−	19	?13
	+	66	19						+	19	?13
	0	393	129								
	−	236	?13								
	+	707	129								

0 = Control. − = Hypothyroid. + = Hyperthyroid. Haem. = Haemorrhage. Necr. = Necrosis.

Comparison between the areas occurring in the hypothyroid (or hyperthyroid) animal and the corresponding control animal was made by the use of the logarithmic ratio. That is, the logarithm of the area in the hypothyroid (or hyperthyroid) animal was subtracted from the logarithm of the area found in the control. The mean of the logarithmic ratios found in the individual tests for each hypothyroid (or hyperthyroid) animal was then calculated. The mean logarithmic ratios are recorded in Table II.

When a "t" test of significance is applied to these mean logarithmic ratios between hypothyroid animals and controls the probability of finding such ratios by chance,

*Research carried out while in receipt of a grant from the Carnegie Trust for the Universities of Scotland.

TABLE II.—*Means of Differences Between Logarithm of Area of Reaction Found in Controls and in Treated Animals (Control minus Treated)*

Group	Means of Differences in Log. Area from Controls			
	Hypothyroid		Hyperthyroid	
	Haemorrhage	Necrosis	Haemorrhage	Necrosis
I	+0·49	+0·75	−0·67	+0·35
II	+0·65	+0·40	−0·37	−0·21
III	+0·10	+0·28	−0·18	+0·15
IVa	+0·73	+0·79	−0·20	+0·13
IVb	+1·17	+1·37		
V	−0·14	+0·05		
VI	+0·49	+0·76	+0·39	+0·87
VII	+1·04	+1·14	+1·22	+1·14
Mean ..	+0·57	+0·69	+0·03	+0·40
"t" test ..	P<0·01	P<0·01	P=0·8	P=0·05

assuming that thyroidectomy had no effect, is $P<0.01$ in the case of area of haemorrhage and $P<0.01$ in the case of area of necrosis. These figures are taken to indicate that a significant difference in area of reaction did occur in the thyroidectomized animals.

The corresponding figures for the hyperthyroid animals are $P=0.8$ for area of haemorrhage and $P=0.05$ for area of necrosis. These latter figures are not considered to be significant.

Results

In the normal sensitized rabbit the skin reaction (Arthus phenomenon) is characterized by the rapid appearance of a wide area of erythema soon followed by oedema. In 12 to 24 hours the central zone of this area shows haemorrhage into it, and within 48 to 72 hours most of this area turns purple or black owing to superficial necrosis.

The different components of the reaction did not appear with the same relative intensity in animals receiving the different treatments. In the thyroidectomized animal the oedema was more solid and persistent. Although the area of haemorrhage relative to area of necrosis was much the same as in the control, the absolute area tended to be less. In the hyperthyroid animal the oedema was thin and evanescent, and, while the area of haemorrhage might be greater than in the control, it was less well defined and less intense. The depth of the necrosis, too, tended to be relatively slight, and was often merely a darkening or mottling of the skin surface. Accurate measurement was therefore difficult.

Quite apart from variables in technique—for example, depth of injection, leakage from the injection track, etc.—the intensity of the Arthus phenomenon depends on at least four factors: (1) the general state of health of the animal; (2) the degree of induced "immunity" to the foreign protein; (3) the level of circulating antibody at the time of testing, the intensity of the reaction being roughly proportional to the precipitin titre (Cannon and Marshall, 1941); and (4) the state of the tissues at the site of injection.

The first and second are obviously related. Not many tests were done, but those confirmed Cannon and Marshall's statement that skin sensitivity runs parallel to antibody titre, as measured by the collodion particle agglutination technique. For any given level of antibody titre skin sensitivity was less in the hypothyroid animals than in the controls. A depression of local tissue reactivity appears, therefore, to be an important factor in the diminution of the response in the former. The large area of thin haemorrhage sometimes observed in the hyperthyroid animals can be attributed to the looseness, vascularity, and lack of fat in the subcutaneous tissues permitting diffusion of the antigen. It is doubtful if this indicates a true increased general sensitivity, since the area of necrosis is not greatly increased, and if thyroid feeding is pushed to extremes the haemorrhage as well as the necrosis diminishes in area.

The conclusion is reached that thyroidectomy in the rabbit diminishes the general hypersensitivity induced by injections of foreign protein. Thyroid feeding has little significant effect.

This opinion is somewhat at variance with the conclusion of Long and Miles (1950), who believe that thyroxine administration increases skin hypersensitivity in tuberculin sensitization in guinea-pigs, while feeding with propyl thiouracil has no effect. A plausible explanation for the increased area of skin reaction in moderate hyperthyroidism has been given above. Their experiment lasted only 60 days after the beginning of propyl thiouracil feeding. After surgical extirpation of the thyroid gland it is only at the end of such a period that the effects of thyroxine deprivation become obvious. During the experiment, therefore, their animals were not markedly myxoedematous.

The experiment described here was abandoned because a respiratory epidemic occurred in the animals. It was observed that any animal about to die, whatever treatment it had received, showed a diminished response compared with the level shown previously while in relatively good health. (For this reason the Table does not include the record of skin tests carried out within a month of the death of any member of the group.) The influence of the thyroid on the allergic response in the rabbit is not thought to be specific. An injurious procedure which interferes with the animal's metabolism in any way can be expected to depress the reaction to a degree proportional to that interference. For example, nitrogen mustard administration diminishes the hypersensitivity response in the rabbit (Bukantz *et al.*, 1949).

Discussion

Implausibility of the Endocrine Theory of Rheumatism

That the rheumatic group of diseases should be the direct result of insufficiency or absence of a specific compound or hormone X (Hench *et al.*, 1949) is contrary to clinical and pathological experience. It has been argued above that the "stress" of hypothyroidism or any other noxious procedure tends to diminish rather than increase the allergic response in the rabbit. Furthermore, in clinical practice rheumatoid arthritis does not afflict only the poorly nourished and poorly housed. Addison's disease is rarely accompanied by rheumatism. Mild streptococcal infections are often associated with rheumatic disease, while severe infections by other organisms show no such association. The survivors of Axis extermination camps did not all develop "stress" diseases, and in the temperate climate of Germany conditions ought to have been ideal for their production.

The rheumatic lesion goes through the inflammatory cycle—necrosis, exudation, organization, scarring—which is quite unlike the primary atrophy that results from endocrine insufficiency. At necropsy there is no histological evidence of degeneration or atrophy of the adrenal.

Before a human disease can be ascribed to insufficiency or absence of a specific compound elaborated within the body most or all of these conditions should be fulfilled. (1) Constant, significant, and specific alteration in the physical or chemical balance of the body fluids or tissues should be shown to exist in all cases. (2) The organ or tissue which is believed to produce the specific compound should show unequivocal morphological evidence of degeneration *post mortem*. (3) The syndrome should be reproduced in the experimental animal by extirpation of or injury to the specific tissue. (4) In the human, when the specific secreting tissue is destroyed by surgery, infection, new growth, etc., the syndrome should be reproduced. (5) The specific compound or a potent extract containing it should have been prepared and shown after administration to restore the chemical and physical balance. (6) The compound by repeated administration should maintain life to the natural term in those afflicted. (7) The compound must be relatively non-toxic and have a high therapeutic ratio.

These postulates are obvious. Myxoedema fulfils all of them, diabetes and pernicious anaemia most of them. Acute rheumatism and rheumatoid arthritis none of them.

To say that rheumatism is the clinical manifestation of an internal metabolic disorder the sequel to stress is merely another way of saying that an animal debilitated by one form of injury is more likely to show a poor reaction to a second injury than one not subjected to the first. This can hardly be called a new theory.

Lack of Specificity of Action of Cortisone

Although the supposed rational basis for the treatment of rheumatic disease by A.C.T.H. and cortisone is difficult to accept, what must be accepted is that these drugs do temporarily relieve if they do not "cure" rheumatoid arthritis. Previously, the most plausible explanation of the pathology of rheumatic disease was the bacterial allergy theory. If one accepts this theory, then by analogy with the experimental animal one would expect that a deleterious procedure induced in a patient with this disease would produce a diminution of the allergic response—a diminution of joint pain and oedema. That the treatments claimed to be effective before the introduction of cortisone were of this nature there is little doubt. Streptococcal vaccine, T.A.B., injection of foreign protein, gold, radiotherapy, all did the same thing equally well, if given in doses of equal toxicity (especially if accompanied by strong psychological suggestion).

It is not unreasonable to argue, therefore, until evidence to the contrary is produced, that A.C.T.H. and cortisone in the dosage used in rheumatoid arthritis are merely another two drugs which are effective, but only effective in toxic or near-toxic doses. One fact in cortisone therapy stands out above all others. Although the therapeutic effects are rapid and dramatic they cannot be maintained, because so-called "toxic side-effects" necessitate withdrawal of the drug.

In my opinion cortisone is effective not because it restores the equilibrium to an unbalanced endocrine system but because it completely upsets the balance of a relatively normal endocrine system.

That this interpretation has to be seriously considered is further demonstrated by the experimental and clinical evidence. Wells and Kendall (1940) have shown that cortisone has a depressant effect on general body growth. It depresses the formation of granulation tissue (Ragan *et al.*, 1949). Cortisone impairs antibody formation (Germuth and Ottinger, 1950). A.C.T.H. inhibits bone growth and causes atrophy of the marrow (Baker and Ingle, 1948). Adrenal cortical extracts (Law and Speirs, 1947) or cortisone (Heilman and Kendall, 1944) retard the growth of lymphoid tumours in animals, and in humans (Taylor *et al.*, 1950), and so on. The chemotherapy of rheumatism has followed the same road as the chemotherapy of cancer (Lees and Lees, 1950).

The liver more than any other organ can claim to be regarded as the central storehouse and factory of the organism. By our thesis, depression of its function would lead to relief of the local symptoms in rheumatoid arthritis. Whether a particular degree of liver damage is produced by the injection of the virus of infectious hepatitis, or by injections of lead, gold, or arsenic, or by a good dose of *x*-ray sickness, or by pregnancy producing a relative deficiency of lipotropic factors, or by injections of cortisone, the therapeutic effect will be the same. It has been ignored that many of the effects of large doses of A.C.T.H. and cortisone in men and animals are mainly depressant, non-specific, inconstant, and affect a wide variety of body functions.

The therapeutic effects of cortisone have been brought as evidence to support the endocrine theory of rheumatism. It is pointed out that they are equally strong evidence for the allergic theory. It all depends on the primary assumption with which the investigator starts.

Future of Cortisone

It is not implied that cortisone and A.C.T.H. are not potent hormones which might have wide therapeutic uses. But it does not follow that physiological doses are therapeutic, nor that the therapeutic effects are mediated through the same mechanism. These drugs have a rapid effect and are rapidly destroyed, so that administration is more easily controlled and cumulative effects are avoided. What specificity these drugs might have is possibly due to their catabolic (Sprague *et al.*, 1950) or "anti-anabolic" (Albright, 1942–3) effect interfering with protein synthesis and turnover, and, if the allergic theory is accepted, by preventing the formation of antibodies and by reducing local tissue reactivity.

It has still to be shown that the end-results of treatment of rheumatism by strong suggestion, physiotherapy, and cortisone are superior to those of strong suggestion, physiotherapy, and other drugs.

In these circumstances is the great cost of cortisone treatment justifiable? What has the large sum spent on cortisone research contributed to our knowledge of the fundamental nature of the rheumatic process?

Summary

Thyroidectomy impairs the allergic skin reaction in rabbits rendered hypersensitive to a foreign protein (horse serum).

This impairment of the allergic response is not specific for thyroidectomy and can be produced by other noxious procedures which derange general metabolism.

It is therefore suggested that the action of A.C.T.H. and cortisone in the rheumatic and hypersensitivity diseases is a toxic one and is not specific.

I am grateful to Dr. Walter M. Levinthal, bacteriologist to the Royal College of Physicians Laboratory, Edinburgh, for much time spent on instructing me on the problems of protein allergy; also to Miss A. M. Scott for technical advice and assistance during the conduct of the experiment.

REFERENCES

Albright, F. (1942-3). *Harvey Lect.*, **38**, 123.
Baker, B. L., and Ingle, D. J. (1948). *Endocrinology*, **43**, 422.
Bukantz, S. C., Dammin, G. J., Wilson, K. S., Johnson, M. C., and Alexander, H. L. (1949). *Proc. Soc. exp. Biol., N.Y.*, **72**, 21.
Cannon, P. R., and Marshall, C. E. (1941). *J. Immunol.*, **40**, 127.
Germuth, F. G., and Ottinger, B. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 815.
Heilman, F. R., and Kendall, E. C. (1944). *Endocrinology*, **34**, 416.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
Law, L. W., and Speirs, R. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 226.
Lees, T. W., and Lees, J. C. (1950). *Cancer*, **3**, 580.
Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W. (1949). *Proc. Soc. exp. Biol., N.Y.*, **72**, 718.
Sprague, R. G., Power, M. H., and Mason, H. L. (1950). *J. Amer. med. Ass.*, **144**, 1341.
Taylor, S. G., Ayer, J. P., and Morris, R. S. (1950). Ibid., **144**, 1058.
Wells, B. B., and Kendall, E. C. (1940). *Proc. Mayo Clin.*, **15**, 324.

The value of organized activity in combating illness of the mind was emphasized by the Minister of Health when he opened a new occupational therapy department at Graylingwell Hospital, Chichester, on August 8. He said that it was a pity that only the less attractive side of life in our mental hospitals—often the problems created by old, inconvenient, and cramped buildings and shortage of staff—attracted public attention. Yet there was a bright and encouraging side about which more should be heard. The encouragement of occupational therapy was now accepted as a natural corollary to the medical and social aspects of treatment. The Minister said that one of the most encouraging features of the report of the Board of Control for 1951 was the fact that more and more mental patients were seeking voluntary treatment. "Obviously the chances of recuperation and recovery are greatly enhanced if the patient is prepared to co-operate fully and freely with those responsible for the necessary medical or psychiatric treatment," he added.

NEMATODES, NERVOUS DISEASE, AND NEUROTROPIC VIRUS INFECTION

OBSERVATIONS IN ANIMAL PATHOLOGY OF PROBABLE SIGNIFICANCE IN MEDICAL NEUROLOGY

BY

J. R. M. INNES,* Sc.D.(Cantab), D.Sc., Ph.D. M.R.C.V.S.

(From the Foundation of Applied Research, San Antonio, Texas)

AND

C. SHOHO, D.V.M.

(Formerly working at the Institute for Infectious Diseases, Tokyo University, Japan)

Beautyman and Woolf (1951) dealt with observations on a child in whom an ascaris larva was found in the brain along with acute poliomyelitis of the brain-stem. These findings might be important for the reasons given by them—namely, that the worm might have facilitated the virus infection, or that there might be a complex virus–helminth relationship as exemplified by the work of Shope (1943) on swine influenza, virus infection being interdependent on the lung-worm and the earthworm. Another point is that there were no neurological signs referable to the larval thalamic lesion, but that neural larval migration might result in occasional cases of focal and generalized epilepsy. They referred to the paucity of pathological reports on nematode invasion of the nervous system of man, but some relevant studies on veterinary pathology inadvertently received no comment. For obvious reasons it usually takes a long time before work in the latter category receives medical notice—inaccessibility of veterinary journals playing some part. Yet examples could be given in which studies on animal diseases were the starting-point in the identification of analogous human disorders. A classic example might be the observation by Griffith Evans (1880) that a trypanosome caused surra of horses in India; Ronald Ross admitted a debt to that work in his famous monograph on malaria, and it must have influenced Bruce, Dutton, and Castellani in the later work on African trypanosomiasis in animals and man.

Epizootic Cerebrospinal Nematodiasis

Initially, we deal with a specific nervous disease of animals which has occurred as a seasonal epizootic in the Orient, and which is caused by immature nematodes (*Setaria digitata*). Great credit for this contribution must be given to Japanese workers. For full accounts of the disease—now called by us epizootic cerebrospinal nematodiasis—with all appropriate Japanese literature, see Shoho (1952), Innes, Shoho, and Piliai (1952), and Innes and Shoho (1952); another paper by Innes (1951) dealt specifically with the same disease in goats in Ceylon.

This epizootic neuroparalysis has occcurred in domestic animals in Japan, Korea, and Ceylon for many years. It is not an uncommon disorder, and it is not one in which nematodes on rare occasions accidentally wander into the nervous system. Indeed, we contend that, if Japanese B encephalitis deserves the title "epidemic," then animal nematodiasis should be preceded by the word "epizootic." It occurs in the summer and autumn, coinciding with the insect vector season. The animals suffer from an acute or subacute paralysis of all four limbs or only the hind limbs, and this is unaccompanied by constitutional signs. Some die quickly, others linger a few weeks, and some recover with residual neurological defects, and in view of what is known about the pathology all these clinical variations are understandable.

The essential pathological process is that of a focal encephalomyelomalacia, which in many cases proceeds within a few days to liquefaction and cavitation. The latter may be only microscopic, but one of us (C. S.) has also seen gross cavities. The lesion may be single or there may be a few, but rarely are there disseminated lesions. The focal process may attack any part of the nervous system in a seemingly haphazard manner. Haemorrhage is inconstant, for this would depend on the migrating nematode striking vessels; hence the lesion itself, wandering in a tortuous microscopic path, might be difficult to detect macroscopically. In several goats from Ceylon the whole nervous system was embedded for section-cutting—in the cord, transverse cuts alternating with longitudinal ones. This indicates the possibly arduous nature of pathological examination which might be required for identification of the disease (Beautyman and Woolf found no naked-eye changes indicative of larval infestation). Meningeal infiltrations with many eosinophils may be seen, sometimes extending to areas far from the malacic site: random selection of nervous tissue for sections might thus foster the idea that only an eosinophilic/lymphocytic meningitis was present. The total lesion is unlike that found in any viral, bacterial, protozoal, mycotic, toxic, or deficiency disease; nor is it demyelination, for all structures rapidly disintegrate in the centre. The process is an acute malacia in a restricted track followed by secondary degeneration of nerve-fibre tracts, and the gigantic swellings of axis cylinders (Wallerian degeneration) in, around, above, and below the malacia are a predominant feature. These findings are unmistakably diagnostic, and are consistent with our concept that the process is simply a mechanical traumatic effect of a wandering worm—now proved experimentally.

It was proved by Japanese workers that the animal neuroparalysis in Korea and Japan was caused by young worms (*Setaria digitata*). This finding was based on the association of worms with lesions, and later by experimental production of the disease in sheep, goats, and horses. The aetiological concept was first suggested by Fujita, and amplified and proved experimentally by Niimi and Kimura (1939–43) and 28 others. A full account is available in a five-volume Report of a Special Research Commission (1939–43), but unfortunately an English translation is not available. Our other papers summarize all these studies, while in the caprine paralysis in Ceylon, McGaughey (1951)—at our instigation—subsequently demonstrated the causal setaria. The name given now is appropriate—namely, epizootic cerebrospinal nematodiasis—for it is better than the original Japanese label of setariasis, and we think other filaria or immature nematodes might be involved in production of the same pathology in the same or different species. The *natural* host of *Setaria digitata* is cattle, in which the adults reside in the abdominal cavity without any visible pathological effect, and in which species microfilariae finally enter the blood.

In the Orient the vectors of the worm are mosquitoes, and the very same species are listed as vectors of Japanese B encephalitis. The microfilariae, on being taken up by the insects, mature in about 14 days as infective larvae, which on passage into *unnatural hosts* (sheep, goats, and horses) migrate by direct routes to the nervous system, and therein produce the damage described. The difficulties of determining the helminthic cause are significant. *Setariae*, like all filariae, are notorious wanderers, and in affected animals, having produced a lesion, may straggle away and be found not in the nervous tissue but in the cerebrospinal fluid. It may also be impossible to recognize parasites in the nervous system of animals with a chronic history of paralysis; for, apart from their wandering, they may dis-

*Aided by a grant from the National Multiple Sclerosis Society, New York.

integrate or calcify, or only remnants of a hyaline capsule may be found. Moreover, if a lesion is not detected macroscopically, the nervous system, even of the sheep or the goat, is a big organ in which to find a small worm.

We now turn to observations by Beautyman and Woolf, and how these cut across the paths of those in animal pathology.

Clinically Inapparent, or Masked, Helminthic Infection of the Nervous System

This phenomenon (Beautyman and Woolf) is supported by observations on nematodiasis. As the malacic lesion is approximately the same size (whether in sheep, goats, or horses) it is clear that clinical signs might depend primarily on the neuro-anatomical location of the focus. In animals with a voluminous nervous system (and enormous length of cord), as in the horse, however, few or no nervous signs might eventuate if the lesion was located in some parts of the cerebral cortex or lower lumbar region of the cord; a minor degree of neurological upset might, indeed, never be spotted. The malacic lesion must be the immediate reaction; a granulomatous one might be the residual, more chronic, effect, in which the parasite might be dead. Consequently, unless the paralysis was immediately fatal, neither the malacic lesion nor the parasite might be recognizable in animals (or man) if life was prolonged. Tanaka *et al.* (1945), in a pathological survey of the brains of 100 *old* horses, found lesions with and without parasites in nine animals in which no clinical signs were seen during life. This same problem of clinically inapparent disease in the presence of even disseminated encephalitic lesions in lower animals has been raised also in experimental allergic encephalitis in mice by Olitsky *et al.* (1950), in guinea-pigs by Lumsden (1949), and by personal observations. The most careful neuropathological examination in such animal conditions thus becomes almost imperative.

Nematode Infestation Facilitating Virus Invasion of the Nervous System

So far as neurotropic virus infections are concerned this problem has not been seriously considered. Shope (1943), however, opened the way by his fascinating work proving that the complex pathogenesis of swine influenza was bound up with earthworm, lung-worm, virus, and *Haemophilus suis*. (See also the work of Syverton *et al.* (1947) on the association of *Trichinella spiralis* and lymphocytic choriomeningitis in guinea-pigs.) Our speculations on a possible parallel adjuvancy between *Setaria digitata* (and the disease) and Japanese B virus encephalitis are no more flights of fancy than those of Beautyman and Woolf. Sabin, Ginder, and Matumoto (1947), in a study of the epidemiology of Japanese B encephalitis, indicated that the virus was sometimes spread extensively in domestic animals in endemic regions of Japan when human beings were affected very little. The problem of how the virus maintains itself in nature during non-epidemic years was considered of profound significance, and they raised the question of intermediate arthropod and helminthic hosts, but without specification. The same mosquitoes have been incriminated in the transmission of Japanese B encephalitis and in nematodiasis of animals, hence an interrelationship cannot be dismissed lightly.*

Dual Neurotropic Virus and Helminthic Infections

If a helminth lodges in the nervous system the final outcome will depend partly on its neuro-anatomical location, and perhaps partly on survival of the worm to continue its damage. That neurological signs can be masked by a later or simultaneous virus infection has been proved by Beautyman and Woolf. In a routine pathological examination of the brains of 69 horses naturally infected with Japanese B (equine) encephalitis, Sugawa, Mochizuki, and Yamamoto (1949) found a malacic lesion with and without setaria in four cases. Consequently, we might ask how often this has happened before: if clinical and other evidence pointed to virus encephalitis, then presumably little further study would be made of the cases but to keep nematodiasis in mind; yet that condition might be of significance. We believe that in Japan neural nematodiasis of animals has often been confused with virus encephalitis, particularly if too much reliance is placed on clinical data and even on neutralization tests. The latter could be positive in the presence of a coincidental nematodiasis; or, indeed, the virus infection might be facilitated through this. It is thus interesting to find, in some reports on the pathology of human Japanese B encephalitis, mention of "mushy areas" in the spinal cord, but it is not certain that these foci received specific histological study. Further, one of us (C. S.) has observed cavitation in the brains of four children reputed to have died from Japanese B encephalitis—a finding which points to the existence of some coincidental process, or an as yet undescribed pathological feature of Japanese B encephalitis.

Migratory Paths of Helminths to the Central Nervous System

Beautyman and Woolf discuss this with particular reference to the classical work of Yokogawa (1923) on ascaris, and therefore emphasis is laid on intravascular paths. It is generally accepted that ascarids, after the hatching of the eggs in the intestines, go on a tour to the lungs and that some larvae may wander into the general circulation and reach the nervous system or the eyes. Yokogawa's original experimental findings, in which 10 out of 14 mice (given a large number of canine ascaris eggs) showed haemorrhages of the cerebrum due to migrating larvae, were also interpreted to mean that the route was via the circulation. We wonder why a direct pathway cannot be considered to account for all such cases.* In cerebrospinal nematodiasis it can hardly be questioned that the direct tissue path is the one taken by setariae, for the malacic lesion is not embolic in nature but mechanically traumatic. We might draw attention here to some obscure work by von Brand and Cullinan (1943), who showed that strongylid larvae of fish, when transplanted into unnatural hosts (rats and chickens), invaded the nervous system and paralysed and killed the latter. These larvae took the direct route, for one could trace the histological path through connective and muscle tissue, and between vertebral joints to the cord, revealed by the granulomatous eosinophilic tissue reaction. The problem of what parasites do in unnatural, as compared with natural, hosts might be the crux of many problems. The thesis that the nervous system (and eye perhaps) may be a strange anatomical site of attraction in unnatural hosts receives further support from Tiner (1951), who reported 100% mortality in white mice from damage to the brain, following infection by ascarids derived from racoons.

Possibility of an Analogous Cerebrospinal Nematodiasis of Animals Occurring in Man

This has been covered fully in another paper (Innes and Shoho, 1952), but the brief explanations given show how such a disorder could evade both accurate clinical and pathological detection—in fact, if patients lived diagnosis might be impossible. Skin and complement-fixation tests, using setaria antigen, might, however, be usefully employed. There are many reports in medical literature reminiscent of the animal disease, grouped under such vague headings as

*The fact that a nematode, and its lesion, are found in one part of the nervous system and evidence of virus infection is found in another would not necessarily exclude a connexion. A nematode could act as a destroyer of the blood–brain barrier in one region and thus facilitate virus invasion, and then wander out and away and penetrate another region when a stage of viraemia was over.

*Reference has been made to the occasional need for a far more careful neuropathological examination than that made in a routine pathological survey of the nervous system. In the case of Beautyman and Woolf, for example, it would have been of the greatest interest to know whether the nematodal lesion in the thalamus was linked to the pia mater by a connected or disconnected glial scar track.

subacute necrotizing myelitis, asymmetrical haemorrhagic encephalopathy, degenerative softening, and so on. We especially draw attention to reports of eosinophilic meningitis with focal malacia—with clinical acute paralytic signs (or those of transverse myelopathy) and a complete absence of evidence indicative of cause (virus, bacteria, or any other—but helminths never considered). It is even conceivable that some cases of reputed disseminated sclerosis, with predominant spinal signs, which do not progress after a primary paralytic attack could be of this nature. A study of the reported data in veterinary pathology might conceivably help to a better understanding. The observation of asymmetrical cerebral cavitation (caused by nematodes ?) in newborn and young calves by one of us (C. S.) might raise speculations in other directions; for multicystic degeneration in the brain of newborn and young children, of unestablished cause, is adequately dealt with in neuropathological literature.

Conclusion

Finally, some indirect support for our ideas arises from Wilder's (1950) work on human endophthalmitis. In 46 eyes of children and adolescents, received from many parts of the U.S.A., a variety of original diagnoses had been made; all showed some features of an eosinophilic or granulomatous lesion, but in none of the original sections were worms present. Serial sections (in one eye—2,300 slides) revealed the finding of a larva in 24 eyes, and the changes were so uniform in type that a diagnosis of nematode endophthalmitis was made for all 46. This disease has an exact analogy in an ocular disease of horses in India, known almost from antiquity, and is caused by *Setaria (digitata ?)*; peculiarly enough, it is sometimes associated with paraplegia (Kumri), which we think is cerebrospinal nematodiasis. Perhaps such human helminthic ocular lesions are no more than an extension in sequence and location of intracranio-vertebral nematodiasis—that is, helminthic parasites can enter the eye via the cranial cavity. In Japan, ocular filariasis in horses is also common, and is also caused by *Setaria digitata* (see Kume, 1951), but onset is about a month later in the year than that of the nervous disease, and both may occur together. This same probability might be remembered in human medicine.

REFERENCES

Beautyman, W., and Woolf, A. L. (1951). *J. Path. Bact.*, **63**, 635.
Evans, G. (1880). In H. H. Scott's *History of Tropical Medicine*, 2nd ed., 1942.
Innes, J. R. M. (1951). *Brit. vet. J.*, **107**, 187.
—— and Shoho, C. (1952). *Arch. Neurol. Psychiat.* (in press).
—— —— and Pillai, C. Perumal (1952). *Brit. vet. J.*, **108**, 71.
Kume, S. (1951). *Recent Advances in Veterinary Science*, p. 186. University, Tokyo. (In Japanese.)
Lumsden, C. E. (1949). *Brain*, **72**, 517.
McGaughey, C. A. (1951). *Brit. vet. J.*, **107**, 449.
Niimi, D., and Kimura, T. (1939-41). *Trans. Soc. path. jap.*, **29**, 466; **30**, 539; **31**, 609. (In Japanese.)
Olitsky, P. K., Casals, J., and Tal, C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 276.
Sabin, A. B., Ginder, D. R., and Matumoto, M. (1947). *Amer. J. Hyg.*, **46**, 341.
Shoho, C. (1952). *Jap. J. exp. Med.* In press.
Shope, R. E. (1943). *J. exp. Med.*, **77**, 127.
Sugawa, Y., Mochizuki, H., and Yamamoto, S. (1949). First report on Japanese Equine Encephalitis. Government Experimental Station for Animal Hygiene, 9.
Syverton, J. T., McCoy, O. R., and Koomen, J. (1947). *J. exp. Med.*, **85**, 759.
Tanaka, T., Suu, S., Shoho, C., and Yamagiwa, S. (1945). *Jap. J. vet. Sci.*, **7**, 117.
Tiner, J. D. (1951). *J. Parasitol.*, **37**, Sect. 2, Suppl. 21.
von Brand, T., and Cullinan, R. P. (1943). *Proc. helminth. Soc. Wash.*, **10**, 29.
Wilder, Helenor C. (1950). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **54**, 99.
Yokagawa, S. (1923). Taiwan Igakkai Zasshi (*J. Formosan med. Ass.*), pp. 226, 241. (In Japanese.)

A note in the *Royal Army Medical Corps News* reports that Sir Almroth Wright's work at the Royal Victoria Hospital, Netley, has been commemorated by the erection of a plaque in the main hall of the hospital. Sir Almroth was at one time professor of pathology in the Army Medical School, and made the first trials of anti-typhoid inoculation on himself and the surgeons on probation in the laboratory of the hospital between 1895 and 1898.

HEREDITARY METHAEMOGLOBINAEMIC CYANOSIS

BY

ANTOINE CODOUNIS, M.D.

From the 3rd Medical Clinic, Red Cross Hospital, Athens, Greece

The increased interest in heart surgery, as introduced by Tousin, Gross, Blalock, d'Allaines, Bonzelot, Lenègre, Soulie, Karayannopoulos, Tountas, Karageorges, and Papanicolis, has drawn attention to the problem of cyanosis as a whole, and not merely as a symptom of congenital malformation of the heart. In a series of investigations of the various cyanotic conditions which I have been carrying on with my associates, Drs. Loucatos and Loutsides, since 1946 (Codounis, Loucatos, and Loutsides, 1947, 1948; Codounis, 1948, 1949), a morbid autonomous entity of the red corpuscle has been defined which we have called "hereditary methaemoglobinaemic cyanosis" (H.M.C.) and which has been increasingly attracting medical attention.

Since 1844, when François described the first Belgian cases of cyanosis without cardiopathy, only 19 similar cases had been noted in the literature up to 1945 by Sievers and Ryon, including their one case and the two of Lian and his co-workers. With the addition of single cases by Graybiel *et al.* and Barcroft and his associates, the total recorded cases of this kind of cyanosis was raised to 21 by the end of 1945.

In 1946 we added our 14 cases of the Vaftochilary family (Chart 1), demonstrating definitely for the first time the hereditary mode of transmission of congenital and familial methaemoglobinaemic cyanosis. At the same time we completed the study of its clinical, biological, and therapeutic aspects. Confirmation of our conclusions has come from Bensis, Gouttas, Pyrros, and Vacrinos (Athens Medical Society, 1947); King, White, and Gilchrist (1947); Gibson and Harrison (1947), who published five cases in a family of nine; and Lutembacher (1949), who found six similar cyanotic cases in four generations of one family. A case has also been reported by Fisher and Wide Price (1949).

Having had occasion during the last two years to study a new genealogical tree comprising 85 members who lived throughout Southern Greece, including 10 born cyanotics, I thought it might be of interest to present this study with a summary of our investigations as a whole. I hope that this research will adequately elucidate this genotypic disease of the blood and differentiate it from other cyanotic conditions.

A New Family Tree

In the study of our second family tree (Chart 2), the Melaniarides (a nickname given the family by people of the district who were impressed by their unusual colouring: *melani*, ink; *vafo*, colouring; *helos*, lips) we followed the system used in that of the Vaftochilary family. Convinced after a series of clinico-biological tests that the two cyanotic sisters—Nos. 7 and 8 of this tree—who came to see us in October, 1949, with a diagnosis of congenital heart disease were actually H.M.C. cases, we thought it wise to undertake a special investigation in order to reach 85 members of the different families of this tree spread over a number of

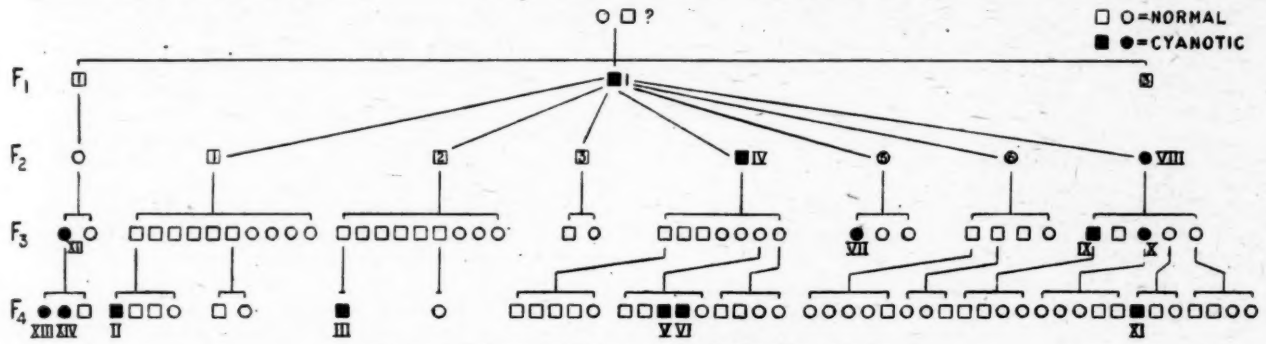


CHART 1.—Genealogical tree of the Vaftochilary family.

villages in the Peloponnese. This investigation had two objectives: to complete our information, and to examine and confirm facts concerning those living subjects suffering from cyanosis—their husbands and wives, their ancestors and descendants—and inquire about the dead. We had to travel long distances by foot or on mule-back over rough terrain. It was thus possible for us to study points of clinical and laboratory interest and to examine spectroscopically the living cases Nos. 2–10 of the third, fourth, and fifth generations.

Case 1 of the first generation died of old age at 80, and we collected data from the country doctor and older persons who had known him. Our investigations also included the husbands or wives unaffected by the disease and other unaffected relatives, not only clinically but spectroscopically, in order to detect methaemoglobin in the blood. This test was negative for all non-cyanotic cases.

1. Branch A

From the first couple of the Melaniarides family two daughters and one son were born, who constitute the first generation (F_1). We do not know which of the two parents transmitted the morbid trait to the later generations of this tree.

The two daughters of this first generation present no apparent cyanosis. The son, however, cyanotic No. 1, ancestor of five successive generations of Branch A, had suffered, according to information given by the country doctor and others, from a very marked cyanosis ever since his birth. Despite the disease he had attained the age of 80 when he died. He was the father of two sons and one daughter, none of whom showed any signs of cyanosis. The disease, however, skipping a generation, was transmitted through his two sons to his grandchildren (F_3). One of his sons, although not cyanotic, transmitted the morbid trait to his only son in a very noticeable degree (No. 2—F_3). The other, although having inherited the morbid trait in a latent manner, did not transmit it directly to any of his children—two sons and one daughter—but through one of his carrier sons to his granddaughter (No. 3—F_4). She in turn married a healthy individual of Branch C of this tree (we shall see further that this branch gave rise to no cyanotics whatsoever), and transmitted the disease directly and to a morbid degree to one of her sons and one of her daughters out of a family of five (Nos. 4 and 5—F_5). This branch has thus produced five cyanotics out of 21 members.

2. Branch B

This branch comprises 47 members spread through four generations. They are the descendants of sister B of cyanotic No. 1, whose descendants we have just studied up to the fifth generation. This branch is of particular interest. It has, like Branch A, produced five cyanotics—No. 6 in the F_3 and Nos. 7, 8, 9, and 10 in the F_4. Considering all that has preceded, we must conclude that the morbid trait was transmitted by sister B, and that she must have been a carrier in the latent stage.

This carrier B of the first generation married an unaffected individual, gave birth to three sons and two daughters, and transmitted the disease in a latent stage to only one of the three sons. The latter, father of five sons and two daughters, transmitted the cyanosis to a marked degree to one of his daughters (No. 6—F_3) and in a latent form to one of his sons. This son married a normal individual, had four daughters, of whom three were complete cyanotics from birth (Nos. 7, 8, and 9—F_4), and two sons, of whom one was also a cyanotic from birth (No. 10—F_4).

It is noteworthy that in this family we find not only the congenital and hereditary character of the disease, but also the familial character, as in the F_5 generation of Branch A. We also met this familial character of the cyanosis in the family tree of the Vaftochilarys.

3. Branch C

Among the 16 members of this branch in four generations, all descendants of sister C of cyanotic No. 1, we have not encountered one single cyanotic. It will be of interest to study later generations in order to see whether they are devoid of cyanosis or will eventually produce some cyanotic condition.

Discussion of the Cases

The members of the Melaniarides family did not intermarry. The disease affects and is transmitted by men as well as women, as is seen in other hereditary diseases such as haemolytic congenital jaundice (Lemy), some kinds of thrombocytopenia, various anaemias such as sickle-cell anaemia, etc. There seems, however, to be a predominance in the male sex in the inheritance of the disease as well as in its transmission.

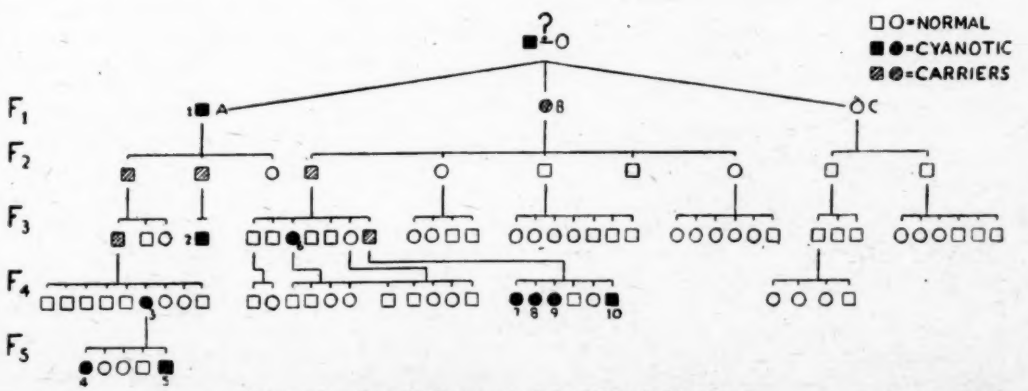


CHART 2.—Genealogical tree of the Melaniarides family.

It is still not known whether in this tree of the Melaniarides family the transmission of the morbid trait follows Mendelian laws, as it does in the Vaftochilary family tree. It appears to be a recessive, as noted by Gibson and Harrison in their case. Lutembacher, Zacopoulos, and we ourselves found cases with inheritance apparently as a dominant character. Thus in four out of five complete genealogical trees of H.M.C. in the literature, the transmission of the morbid trait seems to occur as a dominant, whereas in one (that of the Melaniarides) it seems to be recessive.

In a paper (Codounis, Loucatos, and Loutsides, 1948) we stressed the difficulties encountered by the student of human heredity. In the transmission of morbid hereditary traits several factors and mechanisms are involved, as Butterworth, Kracke, and Riser (1950) also point out in their study on the heredity of spherocytic anaemia in the negro. Therefore, in the hope that fresh studies will further illuminate this field of heredity, we prefer to leave the discussion open concerning the dominant or the recessive mode of transmission of the cyanotic trait.

Since this study 18 cases in two further trees have been discovered by Zacopoulos, a director of the Cardiological Clinic of Military Hospital 423. He suspected that two unrelated soldiers who were patients in his clinic were suffering from cyanosis without cardiac anomaly. He brought them to me, and clinical and spectroscopic blood examination proved that they were actually suffering from H.M.C. One soldier came from Tripolis, in the Peloponnese, and the family consisted of 26 members in four generations, with seven born cyanotics. The other soldier's family tree, in Ptolemais, in Macedonia, consisted of 26 members in three generations, with 11 born cyanotics.

Baltzan and Sugarman (1950) also made a study of a new family tree of four generations which contained 15 cyanotics with inheritance as dominant. This brings the grand total of reported cases up to 92 (see Table). Incidentally, these authors claim to be the first to describe and prove the hereditary basis of this disease, having apparently overlooked all the previous work cited above.

Table Showing the Family Trees of H.M.C. Published from 1946 to 1951

Authors	Nationality	Age	Generations	Members	Cyanotics	Males	Females	Mode of Transmission of the Morbid Trait	Met-Hb		Total Met-Hb (g.%)
									Method of Determining	Amount (g.%)	
Codounis, Loucatos, Loutsides (1946) "Vaftochilary" tree	Greek	6–80	IV	103	14	8	6	Dominant	Spectroscopic		25–30
Codounis, Loucatos, Loutsides (1949) "Melaniarides" tree	,,	6–80	V	85	10	4	6	Recessive	,,		18–40
Lutembacher's tree (1949) ..	French	8–85	V	21	7	2	5	Dominant	,,		—
Zakopoulos's "Tree of Tripolis" (1950)	Greek	18–75	IV	26	7	5	2	,,	,,		10–52
Zakopoulos's "Tree of Ptolemais" (1950)	,,	23–70	III	26	11	5	6	,,	,,		10–52
Baltzan and Sugarman (1950)	Canadian	16–35	IV	33	15	9	6	,,	,,	18–32	15–24

Clinico-biological Aspects of Hereditary Methaemoglobinaemia

On the basis of our experience it is proposed to give a clinico-biological description of this new hereditary disease of the blood, which is an autonomous morbid entity of the red corpuscle.

A. Symptomatology

The dominant clinical symptom which impresses the physician as well as the patient and others is the cyanotic hue, which is violet and sometimes even brownish. The word cyanosis does not always convey a precise idea of the colour of these patients. The hue is usually dichromatic between the blue and the red, or the violet blue and the brown.

The degree of cyanosis is relative to the amount of methaemoglobin present in the blood, varies with each patient, and can be described as light, medium, and marked. Although the cyanosis is ordinarily generalized over the whole body, it is particularly noticeable in the lips, the mucous membrane of the mouth, the tongue, the palate, and the nose, in the cheek-bones and ears, and at the extremities of the fingers and toes, especially under the nails. It may occasionally vary slightly after a muscular effort in some cases, and is a constant characteristic in all patients, being present from birth. Despite the chronic nature of the condition we have never encountered clubbing of fingers, a clinical feature which differentiates it at once from other cyanoses (pulmonary, cardiac, etc.).

As additional symptoms, we note a tendency to dizziness, headaches, dyspnoea (after physical effort), tachycardia, occasional nervous irritability, and, in some cases, general physical weakness. The intensity of these subjective troubles is directly related to the intensity of the cyanosis.

The light form of cyanosis usually presents no serious subjective troubles except an occasional increase during the winter season, or menstruation and other intercurrent conditions.

Cases of moderate and marked cyanosis often present symptoms of anoxaemia. Headaches are the most common manifestation. These disappear as a rule after an injection of 300 to 500 mg. of ascorbic acid or 50 ml. of a 1% solution of methylene blue in isotonic glucose.

Beside these positive signs, an absence of other signs differentiates H.M.C. from all other cyanotic conditions. Thus physical examination never reveals cardiovascular or pulmonary lesions; arterial blood pressure and venous pressure are usually normal; and radiography and electrocardiography are normal.

Dr. Korylos, Director of the Ophthalmological Clinic of the Red Cross Hospital in Athens, reports: "The cases of H.M.C. which we have examined showed no important ophthalmological signs except a light change in the colour of the retina and the diameter of the capillaries. The retina is of a reddish-blue colour. The capillaries, especially the veins, are enlarged and varicose-like. In one case only, the following noteworthy signs were observed: in the right eye, divergent strabismus due to amblyopia, the lens showing a posteriorly cupped cataract; in the left eye, except for a light congestion of the pupil, nothing abnormal was found."

B. Biochemical Remarks

The characteristic sign of this congenital, familial, and hereditary disease is the constant presence in the blood of intracellular methaemoglobin (Met-Hb), which may be discovered spectroscopically. The Met-Hb is the cause of the cyanosis in this disease in our own cases as well as in those described in the medical literature, with the exception of Lutembacher's, in which, despite the intense cyanosis and other features, the band of Met-Hb was missing from the spectrum.

This absence of Met-Hb, if it be later confirmed by other authors, must lead us to suppose that there can be asymptomatic cases of H.M.C. from which one of the clinical or haematological symptoms may be lacking. A similar case was reported in the case of spherocytic anaemia of the negro by Butterworth and his co-workers. But we wonder

whether Met-Hb was actually absent, because we ourselves would more than once have failed to find it if we had not made special efforts. In such cases one must use for the spectroscopic test: (1) a solution of blood in distilled water in the proportion of 1:20, 1:10, or even 1:5; (2) a strong light to develop the spectrum. It often happens, in fact, that Met-Hb, when present in small quantities, does not give the characteristic band in the red if the solution of the blood for spectroscopic examination is too diluted.

The quantitative measurement of Met-Hb by the Dubost method has given us yields from 25–50% of the total haemoglobin (Vaftochilary family), 18–40% for the Melaniarides, and 10–52.5% for the cases of Zacopoulos. It was always intracellular and never extracellular, and discoverable *in vivo* in the ear lobe.

As regards other blood examinations, occasionally we find a slight increase in red and white blood cells, the haemoglobin is either normal or slightly subnormal, the cells normal, and other blood constituents all normal, like the W.R. Urine analysis has also usually been normal.

We have failed to find any correlation whatsoever between this methaemoglobinaemia and blood groups, including the Rh factor. In a certain number of our patients we found a decrease below 0.40 mg. ascorbic acid per 100 ml. of blood. This C-hypoavitaminosis was confirmed by the saturation method.

C. Prognosis

The prognosis of H.M.C. is good, since most of the patients reach an advanced age.

D. Treatment

Although convinced of the hereditary nature of the disease, we have also, however, tried the therapeutic means employed in other cyanoses—ascorbic acid and methylene blue—by intravenous injections or orally. The favourable influence of these drugs on the cyanosis as well as on the subjective troubles of the patients and the sometimes spectacular reduction of methaemoglobin to haemoglobin are only temporary, and continuous oral administration of ascorbic acid is necessary. It is interesting, by the way, to note that the patients themselves felt the favourable effect of lemon and orange juice and other foods rich in ascorbic acid.

Although it is true that the light and medium cases of methaemoglobinaemia are symptomless, the cyanosis in itself is nevertheless not very pleasant, especially for young girls. Thus one sees them submitting to an intravenous injection of methylene blue or ascorbic acid (300 to 500 mg.) in order to obtain, usually at the end of 10 minutes, a decoloration which may last 10 to 15 days, and which is made to last by absorbing 10 to 30 mg. ascorbic acid daily if they do not prefer an injection every 10 or 15 days.

Summary

A new genealogical tree of hereditary methaemoglobinaemic cyanosis (H.M.C.) of five generations, comprising 85 members and including 10 born cyanotics, is described.

H.M.C., also known as congenital or familial cyanosis, or methaemoglobinaemic idiopathic cyanosis, is a distinct clinical entity characterized by the presence of methaemoglobin in the blood, and the absence of clubbing of the fingers. It exists from birth and is inherited by both sexes, with a preponderance in men.

It is thus quite distinct from cyanosis due to congenital heart disease or arteriovenous shunt, to polycythaemia, or to drug intoxication.

Although 42 out of the 92 described cases are in Greeks, the condition has been reported from all continents, so far only in white men.

It is a pleasant duty to express our gratitude and thanks to Mr. Constantine Georgopoulos, president of the Hellenic Red Cross, for the encouragement and support which he gave us in the pursuit of our investigations; and also to Professor D. Chondros for his learned advice and for the loan of the precious spectroscope, of which he deprived himself in order that we might make our measurements of methaemoglobin.

REFERENCES

Baltzan, D. M., and Sugarman, H. (1950). *Canad. med. Ass. J.*, **62**, 348.
Barcroft, H., *et al.* (1945). *Clin. Sci.*, **5**, 145.
Butterworth, C. E., Kracke, R. R., and Riser, W. H. (1950). *Blood*, **5**, 793.
Codounis, A. (1948). First International Conference of Hematology. Buffalo, N.Y.
—— (1949). *Sang*, **20**, 195.
—— Loucatos, G., and Loutsides, E. (1947). *Bull. Acad. Méd. Paris*, **32**, 597.
—— —— —— (1948). *Sang*, **19**, 65.
Fisher, B., and Price, J. W. (1949). *J. Lab. clin. Med.*, **34**, 1677.
Gibson, Q. H., and Harrison, D. C. (1947). *Lancet*, **2**, 941.
Graybiel, A., *et al.* (1945). *Bull. Johns Hopk. Hosp.*, **76**, 155.
King, E. J., White, J. C., and Gilchrist, M. (1947). *J. Path. Bact.*, **59**, 181.
Lutembacher, R. (1949). *Presse méd.*, **57**, 276.

METHAEMOGLOBINAEMIA DUE TO NITRATES IN WELL-WATER

BY

W. A. B. CAMPBELL, M.D., M.R.C.P.Ed., D.C.H.

(From the Royal Belfast Hospital for Sick Children)

Since Comly (1945) reported two cases of cyanosis due to methaemoglobinaemia in young infants caused by the ingestion of nitrates in well-water, numerous cases have been reported from Canada and the U.S.A., a few from Belgium, and some from other countries. Ewing and Mayon-White (1951) reported cases found in a rural area of Suffolk, which were the first recorded in the United Kingdom. It is believed that the present case is the first to be detected in Northern Ireland, although the circumstances necessary for the production of the condition must be relatively common in a predominantly rural community such as this.

Case Report

This infant, a female, was born by normal spontaneous delivery at full term; she cried quickly and gave no trouble in the immediate post-natal period. She was breast-fed for three weeks only, and then weaned on account of "insufficient milk." She was put on to feeds of full-cream dried milk, on which she gained weight. One week after receiving the artificial feeds she began to vomit two or three times a day, generally one to two hours after a feed, quite copiously but not very forcefully. She appeared to be in pain before the vomit. Citrate tablets given in the feeds seemed to reduce the vomiting for a week, but it then recurred, and for five days before her attendance at the outpatient department it had been severe. The bowels were opened once or twice a day, the stools being greenish. On the day before attending hospital she was noticed to be blue, almost black, about the lips and finger-tips.

On examination (June 29, 1951) the infant was seen to be well nourished and energetic. There was generalized slate-blue cyanosis, especially over the lips and fingers. The mouth and throat were healthy. No abnormal signs could be detected in the heart or lungs. The abdomen was normal, the spleen could not be palpated, and no pyloric tumour was felt. The association of marked cyanosis with the generally well-nourished appearance of the infant and the absence of signs in the heart or lungs led to a tentative diagnosis of enterogenous cyanosis. Inquiry revealed that the family drew their water from a well on their own farm. The child was accordingly admitted for confirmation of the diagnosis and for treatment.

Investigations.—Unfortunately it was not possible to carry out a blood examination until the following morning, by

which time she had had several feeds in hospital. A specimen of venous blood showed the typical "chocolate" appearance of the methaemoglobinaemia to the naked eye, and, although the clinical cyanosis had decreased even in the 12 hours since admission (without treatment), methaemoglobin was easily detected spectroscopically in a dilution of 1 in 10. The peripheral blood picture showed: Haemoglobin, 76% (Haldane); red cells, 3,580,000; normoblasts, 4 per 100 leucocytes; and polychromasia. Two specimens of fasting gastric juice were taken; the first had a *p*H of 3.8 with no free acid, and gave a growth of coliform organisms on culture; the second had a *p*H of 3.3, no free acid, and was sterile. A sample of the well-water was analysed for nitrate; the following result was obtained: 116 parts per million (as NO_3'); 26.2 p.p.m. as nitrogen. This was reported to the divisional medical officer, who arranged for bacteriological examination of the well-water, and found it to be "unsatisfactory," with 50 coliform organisms of faecal origin per 100 ml.

Progress and Treatment.—As soon as blood samples had been obtained, treatment was started with 50 mg. of ascorbic acid in each four-hourly feed. Cyanosis, which had begun to fade even before treatment, had completely disappeared by the fourth day. The infant gained weight steadily—10 oz. (283 g.) in five days—and was discharged home on July 5, six days after admission, with no signs or symptoms. Arrangements were made by the family to obtain water from a branch of the main Belfast water supply, which passes close to their home. The infant apparently did not feed well after discharge, was irritable, and lost weight—1 lb. (454 g.) in 14 days. The stools became more frequent ten days after discharge and vomiting started on July 18. The child was readmitted, and was found to be very dehydrated and lethargic. There was no cyanosis on this occasion. The condition was thought to be an infective gastro-enteritis, and as soon as the dehydration had been corrected the infant was transferred to the Northern Ireland Fever Hospital, where she had a stormy course, but eventually recovered, being discharged on September 26. No cyanosis was noted while in that hospital. Her progress since then has been uneventful, and she has had no feeding difficulty. Water is still being obtained from a neighbouring farm which has a piped supply.

Discussion

When an infant in the first few weeks of life is found to be cyanosed, the suspicion of congenital cardiac lesions or of some form of respiratory obstruction is likely to arise, and such causes do in fact account for most cases. It is of interest in this connection that Donahoe (1949) states that all five of the cases which he reports had been treated by *x* rays for presumed enlargement of the thymus before the true cause of their cyanosis was established.

Methaemoglobinaemia sufficient to cause obvious cyanosis may be produced in a variety of ways, none of which are really common. Apart from cases of familial idiopathic methaemoglobinaemia (Breakey *et al.*, 1951), in which there is an intrinsic disturbance of the normal enzyme reactions in the erythrocytes, the condition may be caused by a wide variety of extrinsic factors acting on the erythrocytes, either infections or chemical poisons. These may be divided, according to Ferrant (1946), into those producing plasma methaemoglobinaemia—for example, blackwater fever, sepsis (Winckel's disease), etc.—and those giving cellular methaemoglobinaemia, including so-called "enterogenous cyanosis" and a wide range of drugs and other chemicals. The latter not only may be ingested, but in certain cases may be absorbed through the unbroken skin of infants—for example, aniline dyes used for marking napkins or naphthalene moth crystals. Walliker and Baxter (1949) list a large number of these causes and describe illustrative cases.

Comly (1945) is generally recognized as having reported the first cases of methaemoglobinaemia in infants that could be shown to be due to the use of well-water with a high nitrate content in the preparation of artificial feeds. Since then many cases have been added to the literature; those published up to 1950 are reviewed by Lecks (1950). He also describes the clinical appearance of these infants, showing cyanosis, gastro-intestinal upsets, and developing lethargy, progressing to apathy with air-hunger and convulsions in severe cases. There are characteristically few physical signs apart from the cyanosis, and this latter is typically of a "slate-grey blueness," distinguishable from that found in congenital heart disease.

In all cases the water supply has been from a shallow well, easily contaminated, or occasionally a deep well with defective casing. The condition is most likely to occur in infants fed on dried milks, less often on evaporated milk, and least on mixtures of cows' milk and water; this is because the proportion of contaminated water is naturally higher in the first two, and therefore the total amount of nitrate ingested is greater. However, if the cows use the same water supply their milk may contain enough nitrate to be dangerous, and one case is reported by Donahoe (1949) in which cyanosis developed in a breast-fed infant whose mother was drinking contaminated water, the cyanosis disappearing when the water supply was changed.

The actual concentration of nitrate found has varied from 15 to 250 or more parts per million of nitrate nitrogen, usually with traces of nitrite as well. Weart (1948) and Hoather (1951) attempted to relate the nitrate content to the degree of bacterial contamination, but, although most of the samples of water were unsatisfactory from the bacteriological standpoint, no very close correlation could be found. Boiling the water does not affect the nitrate content and therefore it cannot be made safe for use in preparing feeds in this way. Methods have been devised for removing the nitrates (Krueger, 1949), but in most cases it will be more satisfactory to obtain an alternative supply of water.

Adults do not appear ever to be affected by the water, and can drink it with impunity so far as the nitrate content is concerned. Several theories have been advanced to account for the exclusive appearance in infants: Cornblath and Hartmann (1948) found that the gastric juice of affected infants had a low free acid, with *p*H 4 or higher; this permitted the growth of nitrate-splitting organisms higher up the gastro-intestinal tract than is possible in adults, the nitrate thus formed being absorbed in the small intestine. Ferrant (1946) holds that nitrate is normally split to nitrite and then to ammonia before absorption takes place, but that if excess nitrate is given this change cannot take place quickly enough and nitrite is absorbed in significant quantity. This is also held by Medovy *et al.* (1947). Another possible factor is that nitrite forms methaemoglobin more easily with "foetal" haemoglobin than with the adult form.

Treatment is fortunately comparatively simple, and is rapidly effective in all but the most severe cases. In mild degrees of the condition, merely removing the source of nitrate will permit a spontaneous cure in a few days: the case reported above showed clinical improvement within 12 hours of admission to hospital. In moderately severe cases ascorbic acid by mouth or intravenously will produce a cure in 12 to 24 hours. In severe cases methylene blue, given intravenously in 1% solution, 1–2 mg. per kg., will produce clinical cure within 30 minutes.

Relapse can be prevented by feeding the infant on acidified (lactic acid) feeds, but, as the water is likely to be bacteriologically suspect, it is preferable to obtain it from an alternative source.

Summary

A case of cyanosis in a month-old infant, due to methaemoglobinaemia caused by the presence of nitrate in well-water used for preparing feeds, is reported from Northern Ireland.

The infant made a rapid recovery on treatment with ascorbic acid.

It is suggested that similar cases may arise more often than has previously been recognized in rural

areas. Such infants may die if the cyanosis is attributed to congenital heart disease and treatment is not given.

My thanks are due to Mr. D. W. Neill for carrying out the spectroscopic examination of the blood and for estimating the nitrate content of the water.

REFERENCES

Breakey, V. K. St. G., Gibson, Q. H., and Harrison, D. C. (1951). *Lancet*, 1, 935.
Comly, H. H. (1945). *J. Amer. med. Ass.*, 129, 112.
Cornblath, M., and Hartmann, A. F. (1948). *J. Pediat.*, 33, 421.
Donahoe, W. E. (1949). *Pediatrics*, 3, 308.
Ewing, M. C., and Mayon-White, R. M. (1951). *Lancet*, 1, 931.
Ferrant, M. (1946). *J. Pediat.*, 29, 585.
Hoather, R. C. (1951). *Lancet*, 1, 1324.
Krueger, G. M. (1949). *J. Pediat.*, 35, 482.
Lecks, H. I. (1950). *Amer. J. Dis. Child.*, 79, 117.
Medovy, H., Guest, W. C., and Victor, M. (1947). *Canad. med. Ass. J.*, 56, 505.
Walliker, G. W., and Baxter, E. H. (1949). *Arch. Paediat.*, 66, 143.
Weart, J. G. (1948). *Illinois med. J.*, 93, 131.

CUTANEOUS REACTIONS TO INJECTION OF PROGESTERONE SOLUTIONS INTO THE SKIN

BY

VERNON R. PICKLES, M.D., D.C.H.

(From the Department of Physiology, Medical School, Newcastle-upon-Tyne)

It has been noticed that the intradermal injection of progesterone solution causes a complex reaction in the skin—an immediate and transitory "triple response" (Lewis, 1927), followed after about a week by a localized follicular eczema, which on subsiding leaves a pigmented patch. It is known that in different circumstances oestradiol or testosterone may increase skin pigmentation; and the present observations are perhaps mainly of interest in that they provide a further example of such an effect of a sex hormone.

Experimental Procedure and Results

Progesterone solutions were injected into the skin of 29 medical students, 10 being women, and into my own skin. Each received two intradermal injections at points a few centimetres apart on the anterior surface of the forearm; one was of "progestin," containing 1 mg. of progesterone per ml. in ethyl oleate, the other of progestin, 25 mg. per ml. In each case 0.04 ml. was injected, but measurement showed that about half of the oily solution rapidly escaped through the track of the needle. The quantities of progesterone that remained in the skin were therefore about 0.02 and 0.5 mg., and of ethyl oleate 0.02 ml.

In every case a stinging sensation and a widespread flare developed within a minute or two. Wheal formation at this stage was minimal, and (as shown by subsequent tests on one subject) the size of this initial reaction depended on the volume of solution injected, of whichever strength, rather than on the amount of progesterone it contained.

This reaction subsided during the first day, and for the next week many of the subjects showed little evidence of the injection. Then from about the seventh day onwards a further reaction was seen in all but 5 of the 30 subjects. It looked like a small patch of follicular eczema, but it was only mildly irritating. Each "follicle" was the centre of a minute area of brown pigmentation; when the blood was pressed out of the distended minute vessels by means of a microscope slide the pigmentation was more obvious. The pigment was not identified, but throughout all stages of its development and fading it was indistinguishable in colour from that of sun tan. During this period in the summer many of the subjects developed a moderate natural sun tan which overlapped the experimental areas.

When the experimental reaction was at its height, at about the fourteenth day, 13 subjects showed at the site of the injection of the larger amount of progesterone a patch of pigmentation which was judged to be equivalent to a marked sun tan and a further 8 showed one equal to a mild sun tan; the corresponding figures for the smaller concentration of progesterone were 2 and 16 respectively. Although these figures are the result of subjective judgment, there is no doubt that, at this stage, in many cases the pigmentary reaction to the more concentrated solution was greater than that to the less concentrated. Only 4 of the 30 subjects showed no pigmentation whatever.

The occurrence of pigmentation of any degree was distributed evenly among those with fair, medium, or dark hair and skins, but the densest was seen in dark (European) subjects. There was no preponderant incidence in either sex. The pigmentation persisted in most cases for some weeks, although the eczema-like reaction subsided during the next few days.

Then in nine subjects (four men and five women) an unexpected reaction occurred. During the third week after the injection the site, particularly that at which the more concentrated solution had been introduced, became first itchy and then "inflamed," with eczematous follicles and wheals. The surface desquamated and the whole area of about 5-cm. diameter became apparently oedematous and pervaded by the brown pigment. Although half the women showed this more severe reaction, as compared with one-fifth of the men, there was no significant correlation with the phase of the menstrual cycle. The most severe reaction was in a woman. Some subjects had an intense irritation, and the application of adhesive tape to hold dressings in place caused subsidiary foci of reaction. Although the students had by now dispersed and the later stages of the reactions could not be watched personally, it seems that in no case did any infection of the areas occur.

Mepyramine hydrogen maleate ("anthisan") cream gave some relief, but usually was not completely effective. The reactions subsided, in some cases with recrudescences, during the next week or month. The pigmentation tended to fade a little more slowly than the other manifestations.

Further similar injections of the oily medium alone (ethyl oleate) were made into my skin. It was apparent that the initial triple response could be caused by injection of the medium alone. The later eczematous reaction appeared, but in smaller degree, and it was very doubtful whether any pigmentation resulted. Slight pigmentation, however, followed intradermal injection of normal saline. I did not suffer any severe reaction to either the progestin or the ethyl oleate injections; but, inasmuch as the other reactions appeared to be due partly to the medium, and some of the other subjects had experienced unpleasant reactions, it was not felt justifiable to repeat the injections with the medium on the other subjects.

Repetition of pairs of injections, of progestin and ethyl oleate, in my skin during a period of several months gave gradually diminishing responses to both.

Discussion

The evidence suggests that the initial triple response and the eczematous reaction of the second week are non-specific responses to the injection of the oily medium, ethyl oleate. The greater intensity of pigmentation at the site of injection of the concentrated solution, and possibly the whole of the later severe reaction that occurred in 4 of the 20 men and in 5 of the 10 women, seem to depend on the presence of progesterone in the injected solution. Some examples are known of similar effects of sex hormones. The localized hyperpigmentation of pregnancy can be imitated by oral administration of oestrogens (Davis *et al.*, 1945), but the possible participation during pregnancy of other hormones such as progesterone does not seem to

have been excluded. Testosterone is necessary for the full development of pigmentation after ultra-violet irradiation (Edwards *et al.*, 1941). Of other steroid hormones, deoxycortone inhibits the development of melanophores in explanted chick embryo skin (Hamilton, 1940), but does not usually decrease the hyperpigmentation in Addison's disease. Cortisone inhibits pigmentation in black-hooded rats (Whitaker and Baker, 1948), but apparently not in human subjects (Järvinen, 1951). To this list may be added the effect of progesterone described here.

My thanks are due to the medical students who acted as subjects, and to Messrs. British Drug Houses Ltd., who supplied the progesterone solutions.

References

Davis, M. E., Boynton, M. W., Ferguson, J. H., and Rothman, S. (1945). *J. clin. Endocrinol.*, **5**, 138.
Edwards, E. A., Hamilton, J. B., Duntley, S. Q., and Hubert, G. (1941). *Endocrinology*, **28**, 119.
Hamilton, H. L. (1940). *Proc. Soc. exp. Biol., N.Y.*, **45**, 571.
Järvinen, K. A. J. (1951). *British Medical Journal*, **2**, 1377.
Lewis, T. (1927). *The Blood Vessels of the Human Skin and their Responses*. Shaw, London.
Whitaker, W. L., and Baker, B. L. (1948). *Science*, **108**, 207.

Medical Memoranda

Milk Allergy

The following case is worthy of record because of the interesting way in which it presented itself.

Case Report

The patient, a boy aged 4, developed slight eczema of the hands at the age of 2 months. He was breast-fed from birth, and at 7 months weaning was attempted. He showed an immediate distaste for cow's milk, and whenever given it a perioral urticarial rash developed, and his eczema became worse. Many different forms of milk were given, but to all he showed a reaction. Thus he continued being breast-fed until 15 months old, also taking solids and orange juice. He was not given cow's milk or any substitute. He was then seen by a dermatologist, who thought his eczema was due to proteins in the diet, so he was put on a relatively protein-free diet of vegetables, fruit, cereals, orange juice, and a little milk, which always caused a perioral urticarial rash. He was given a little meat, but, although it did not seem to cause a reaction, he did not like it very much. The mother discontinued her visits to the dermatologist after some months, but still kept the child on this diet.

The child was referred to us at the age of 4 years because a medical officer thought he looked undernourished, and found on questioning the mother that during the past few months he had been irritable and easily tired, played games very little, and had to have afternoon naps. Sometimes, though not often, his stools were pale and offensive.

On inquiry from his parents it was found that he was sensitive to the following food, and in addition showed various idiosyncrasies:—(1) Fish: extremely sensitive—even the smell of fish is said to cause a reaction. (2) Milk (goat's and cow's): perioral urticarial rash; eczema worse. (3) Eggs: appear to have a delayed action. (4) Meat: no reaction, but does not like it. (5) Cereals: does not like porridge; likes bread—no reaction. (6) Cheese: does not like it.

His family history showed allergies on the maternal side. His grandmother suffered from asthma, an aunt from eczema, and a cousin from urticaria. His mother herself has eczema and is highly nervous.

On physical examination the boy was very pale, with normal height and weight for his age. His lower eyelids were puffy, and small glands were palpable in his neck. He showed marked eczema of the hands, but no lesions of the skin elsewhere except cracks at the corners of the mouth. No enlargement of liver or spleen was noted.

Blood count: Hb, 75% (10.5 g.) Sahli; R.B.C., 2,800,000 per c.mm. (P.C.V. 27%, M.C.V. 96.4 μ^3, M.C.H.C. 38.8%); W.B.C., 4,800 per c.mm. (polymorphs 61%, lymphocytes 35%, monocytes 4%); reticulocytes, 0.5%; total plasma protein, 5.25 g.%. Stained blood film showed many well-haemoglobinized macrocytes.

Response to Milk.—Under surveillance the boy was given some fresh cow's milk to drink. Within five minutes he developed a well-marked perioral urticarial rash. Later he was given boiled milk, and only a very slight rash appeared. A skin-sensitivity test was carried out, using pieces of lint dipped in boiled and fresh milk. No reaction was observed with the boiled milk.

He was put on boiled milk instead of fresh milk, and was given proteolysed liver extract, folic acid, and "marmite," because of a suspicion that he might have an incipient B-avitaminosis. On this treatment he rapidly improved, and his last blood count, taken 10 weeks later, was as follows: Hb, 94% (12.8 g.) Sahli; R.B.C., 5,150,000 per c.mm. (P.C.V. 42%, M.C.V. 80 μ^3, M.C.H.C. 30.5%); W.B.C., 9,500 per c.mm (polymorphs 50%, lymphocytes 35%, monocytes 6%, eosinophils 8%, basophils 1%); total plasma proteins, 6.5 g.%. His parents stated that he was more active than they had ever known him.

Comment

This boy presented as a case of macrocytic anaemia associated with protein deficiency, having lived for about 2 years 7 months on a diet poor in proteins, especially in first-class proteins.

The most important factor was his allergy to milk, which normally provides the chief source of protein in a child's diet. Milk itself is one of the three commonest food allergens, being second in frequency to wheat, and equal in incidence to egg. For example, in a series of 175 cases of food allergy, Rowe (1931) found 57% due to wheat, 31% to milk, and 35% to egg, the overlapping figures being due to multiple sensitization in some of the patients. Alvarez (1937), in a group of 500 cases of abdominal distress due to food allergies, found 26% due to milk, cream, and ice-cream, and another 5% due to cheese.

In many cases of infants reacting to milk there is a history of milk incapacity in the parents, and, though this was not found in this case, there was a strong family history of eczema. The diagnosis of milk allergy in infants and children rests on the history and the therapeutic test of withdrawal of milk from the diet. Scratch skin tests have been used, but they are of small value as an aid to diagnosis.

In one series of 65 cases of milk eczema in which scratch skin tests were carried out, only 5 were positive to cow's milk (Kerley, 1936). Kerley has classified persons subject to milk reactions into (1) those who suffer from shock through ingestion; (2) those with gastro-intestinal symptoms; and (3) those with skin reactions—eczema and urticaria. At least two deaths have been reported in the shock-reaction group (Finkelstein—see Kerley, 1936). My case obviously falls into the third group.

Studies on milk allergy by Ratner (1935) have shown that the heat-labile elements in the milk (lactalbumin and lactoglobulin) are responsible for practically all cases, so that some form of heat-treated or chemically denatured milk can be safely used. Skimmed fresh cow's milk, cooked for several hours, is said to supply the best desensitized milk product for use in eczema of infants (Kerley, 1936). The skimming removes the fat, which either interferes with the desensitizing process or adds an element that bears on the production of the eczema. It is sometimes found, though it was not true in this case, that goat's milk does not give a reaction.

SUMMARY

A case of macrocytic protein deficiency anaemia in a boy suffering from milk allergy (eczema and urticaria) is described. He was able to take boiled cow's milk. The literature is briefly reviewed.

My thanks are due to the Director-General, R.A.F. Medical Services, for permission to publish this case; to Air Vice-Marshal T. St. C. Morton and Wing Commander W. P. Stamm, of the Institute of Pathology and Tropical Medicine, R.A.F., Halton, for interest and guidance; and also to Flight Lieutenant Watson, who sent this boy to the laboratory for examination.

W. F. WALKER, M.B., Ch.B.,
Squadron Leader, Royal Air Force.

REFERENCES

Alvarez, W. C. (1937). *Proc. Mayo Clin.*, **12**, 88.
Kerley, C. G. (1936). *N.Y. St. J. Med.*, **36**, 1320.
Ratner, Bret (1935). *J. Amer. med. Ass.*, **105**, 934.
Rowe, A. H. (1931). *Food Allergy*. Lea and Febiger, Philadelphia.

Two Cases of Acute Idiopathic Porphyria

A number of cases of acute idiopathic porphyria have been reported in the literature in recent years, but we think the disease interesting and rare enough to merit the recording of two further cases.

CASE 1

The patient, a single woman aged 20—height 5 ft. 8 in. (173 cm.), weight 6 st. 6 lb. (41 kg.)—was first admitted on June 18, 1948, as an acute abdominal emergency. She gave a history of five days' colicky upper abdominal pain—the onset coinciding with a period—nausea, and obstinate constipation. She had vomited on three occasions. Her past history was negative. Her parents and two siblings were alive and well.

On examination she looked ill. Her temperature was 99.6° F. (37.6° C.), pulse 80, and respirations 20. Her tongue was furred; there was no scleral or cutaneous pigmentation. The abdomen was soft, not distended, and without guarding or local tenderness. Peristaltic sounds were normal. Rectal examination was negative. Heart : apex beat forcible ; no enlargement ; no murmurs ; rhythm normal ; rate 80. The blood pressure was 170/120. Chest and C.N.S.: N.A.D. A few hours later she vomited ; her temperature was 99° F. (37.2° C.) and pulse 72. The pain continued unabated, and laparotomy was performed. No abnormality was found.

After operation the pain persisted. The urine contained a trace of albumin and "excess urobilin," the blood N.P.N. being 70 mg. per 100 ml. During the ensuing week the pain continued, and on the fifth post-operative day she had an epileptiform convulsion. The blood pressure now was 160/100. The white blood cells numbered 31,000 (polymorphs 95%, lymphocytes 4%, monocytes 1%). The urine still showed a trace of albumin with an occasional granular cast. The blood N.P.N. remained at 70 mm. per 100 ml. The chest *x*-ray picture and cerebrospinal fluid were normal, and the blood Wassermann reaction was negative. She remained slightly febrile, and 14 days after operation complained of weakness of the legs. Examination revealed weakness, with muscle tenderness of the proximal muscle groups of both arms and legs. The cranial nerves were normal, and there was no sensory loss. A repeat lumbar tap revealed normal fluid. She now began to improve, the blood pressure falling to 130/80, and she was discharged on September 22. No definite diagnosis was made.

She was next admitted on June 13, 1949, with identical symptoms. The combination of severe abdominal pain and marked hypertension, together with the history of a negative laparotomy, suggested porphyria, and examination of the urine led to quick confirmation. Up to the present she has had five attacks. Each began and evolved in the same manner, and neurological complications occurred in all but one. The last acute episode occurred in January, 1951. She has remained well since, although the urine is often coloured red.

CASE 2

A single man aged 41 was admitted on March 12, 1951. The history was of attacks of lower abdominal pain for four months, becoming more severe in the last three days, and violent eight hours before admission. He was nauseated and constipated.

On examination he was obviously in severe pain. His temperature was 98.2° F. (36.8° C.), pulse 56, and blood pressure 140/90. Some guarding and tenderness in the epigastrium were the only abnormalities noted. After some hours' observation it was decided to explore the abdomen with the possibility of a posterior perforation in mind. Nothing abnormal was found at operation.

Soon after operation he passed port-wine-coloured urine, and spectroscopic examination revealed the presence of porphyrins. On re-examination at this time he had become uncooperative and resentful ; the blood pressure was 185/115, and there was obvious recent wasting of the leg muscles, especially the quadriceps. During the next few days the pain persisted, the blood pressure rose to 205/120, and the patient became deluded and irrational at times. The symptoms gradually abated, and by the 10th day after operation he was symptom-free and co-operative, the blood pressure was 130/80, and the urine was normal in colour.

He was discharged from hospital on April 14, and by that time the wasting of the legs was rapidly disappearing. He has been seen as an out-patient since, and has had no further attacks of pain or staining of the urine.

COMMENTS

Both cases were admitted as acute abdominal catastrophes. The association of severe unremitting colicky abdominal pain with vomiting and obstinate constipation suggests serious abdominal mischief, and in some cases may not unreasonably lead to laparotomy. The abdominal symptoms may be clamant, but are seldom supported by definite physical signs of local or general abdominal disease.

In neither case was a firm pre-operative diagnosis made, and laparotomy was undertaken mainly in the spirit of "it is better to be safe than sorry." The disease, although admittedly rare, is probably commoner than has hitherto been realized, and may well account for many "negative" laparotomies. It is, of course, very pertinent in the differential diagnosis of polyneuritis, Landy's paralysis, and even of some psychoses. As Petrie remarks, "The symptoms of acute porphyria tend to be remarkably stereotyped." This is well exemplified in these cases, particularly in Case 1, in which the story is almost monotonous. Yet the diagnosis on the first three occasions of her admission varied from intestinal obstruction to acute obstructive appendicitis. There is, however, the discrepancy between the symptoms and paucity of signs, which may suggest something unusual. If hypertension and neurological signs are present as well the diagnosis should be easy, but hypertension may not be present, at any rate in the initial stages, and the neuropathy tends to develop a little later. If the disease is not borne in mind the diagnosis will be missed, and this may well lead to an unnecessary laparotomy in a seriously ill patient, liable to serious and possibly fatal neurological complications at any time.

We wish to thank Dr. H. H. MacWilliam, medical superintendent, Walton Hospital, for permission to publish these cases, and Professor B. G. Maegraith and Dr. W. H. H. Andrews, of the Liverpool School of Tropical Medicine, for the urinary assays.

C. J. WILLIAMS, M.D., M.R.C.P.,
Assistant Physician.
K. R. LOTHIAN, F.R.C.S.,
Senior Surgical Registrar.
Walton Hospital, Liverpool.

REFERENCE

Petrie, E. (1948). *British Medical Journal*, **1**, 926.

Reviews

THE KIDNEY

The Kidney: Structure and Function in Health and Disease. By Professor Homer W. Smith, Sc.D., M.S. Oxford Medical Publications. (Pp. 1,049; 153 figures. £5.) New York and London: Oxford University Press (Geoffrey Cumberlege). 1951.

This book embodies the results of many years' study of renal function by an acknowledged master of the subject. In no branch of medicine has knowledge increased more rapidly during the past quarter of a century than in the science of nephrology, and it has long been impossible even for the specialist to keep abreast of the subject in all of its many aspects. The need for a comprehensive and up-to-date survey of what has been learned about the functions of the kidney since the publication in 1926 of Cushny's *The Secretion of the Urine* has therefore long been felt. In this, his latest book, Dr. Homer Smith ably and amply fulfils the need. In a series of brilliant and balanced studies the author continues the story from Cushny's to the present time. There can surely be little that is known about the functions of the kidney that is not to be found in this invaluable work.

It would not be possible in a brief review even to enumerate the many problems so fully and carefully considered here, though mention may be made of some. Perhaps the outstanding advance in the knowledge of renal function in recent years is the recognition of the importance of the conservative, as distinct from the eliminative, activities of the kidney. The author properly emphasizes this throughout the book, and also the prominent role of sodium in renal economics. Renal clearances and their implications are exhaustively discussed, as is to be expected of one who has himself contributed so much to our understanding of them. He squarely faces the vexed questions of renal circulation and innervation, though some of the conclusions reached about the former will not be accepted by all.

This is a book for the expert. The nephrologist and the research worker will find it indispensable. There are no fewer than 2,300 references, and an adequate subject index concludes the volume. In writing it, Dr. Homer Smith has placed the profession, and through it a large section of suffering mankind, incalculably in his debt, and he is to be congratulated on a very remarkable achievement.

A. A. OSMAN.

SURGEONS' EXPERIENCE

The Surgical Practice of the Lahey Clinic. By Members of the Staff of Lahey Clinic, Boston. (Pp. 1,014; 784 illustrations on 509 figures. £3 15s.) Philadelphia and London: W. B. Saunders Company. 1951.

This volume presents a record of ten years' work in a great American clinic, and it offers the peculiar advantage that in that period the methods adopted have been deliberately standardized and are therefore unusually uniform. They may thus be accepted as the conclusions reached by an important body of surgical experience. The whole field of surgery is covered and in every section the newest and most advanced methods are described. The records of 25,000 operations for disease of the thyroid are a testimony to the solid foundation on which these methods are founded and the scale of the surgeons' experience. Only a great organization could have coped with such numbers and reduced their analysis to useful terms.

The volume opens with a magnificent series of articles on the thyroid gland and neck, beautifully illustrated and packed with new material. Every detail is described with precision, and the reader is left in no doubt about the procedures or the reason for their adoption. Founded on a vast experience, it forms by far the most important section of the whole volume. The next section is on the modern surgery of the chest, including the oesophagus, lungs, and heart. It contains much of interest; some of the work is still in the experimental stage and final solutions are by no means determined. Of other articles those on total gastrectomy, on ulcerative colitis, and on stricture of the bile ducts are of great interest, while the series of chapters on the surgery of the brain, the spinal cord, and the sympathetic nervous system reach a high level and deal with many new problems.

But the volume must be studied as a whole to gain any appreciation of the vast amount of original material it contains. It is essentially a work appealing to the expert, and there must be few experts who will not gain from its close study. It provides indeed a frank record of great achievement for which every surgeon will be grateful. It is well produced and beautifully illustrated.

HENRY SOUTTAR.

NERVOUS CONDUCTION

The Electrical Activity of the Nervous System. By Mary A. B. Brazier, B.Sc., Ph.D. A Textbook for Students. (Pp. 220; 96 figures. £1 5s.) London: Sir Isaac Pitman and Sons. 1951.

This book, which is described as a textbook for students, is admirable. It is clearly written and is readily intelligible to those whose knowledge of electricity and of mathematics is slight. The author surveys all aspects of electrical activity in the nervous system, describing the various experimental findings without going into details of the techniques used, which, as she says, can be learned only in the laboratory. Where there are differences of opinion—as, for example, the method of propagation of the nerve impulse—the reasoned arguments in favour of the rival theories are given without prejudice.

The best chapters in the book are those on conduction in peripheral nerves, and the author clearly explains the classical work of Gasser and Erlanger on the varying rates of conduction in fibres of different sizes. Some account is given of the perplexing subject of transmission at synapses, and of electrical activity of the spinal cord and of the organs of special sense, while the last four chapters are on the electrical activity of the brain. The chapters on cortical response to peripheral stimulation and on the normal human electroencephalogram are good, but the chapter on the abnormal electroencephalogram might well be omitted in the next edition. This subject is too large for discussion in a short chapter and hardly falls within the scope of a book on the normal nervous system. There is an excellent reference list at the end of each chapter to encourage further reading.

This book will be essential for all students reading for degrees in physiology, and will be of great value to those students and teachers of neurology who lack the time or inclination to keep up to date with original work on the electrophysiology of the nervous system.

J. W. ALDREN TURNER.

HYGIENE AND DIETETICS

Hygiene, Infectious Diseases, and Dietetics. By Dennis H. Geffen, M.D., D.P.H., and Susan Tracy, M.R.C.S., L.R.C.P., D.P.H. (Pp. 276. 9s. 6d.) London: Longmans, Green and Co. 1952.

This small textbook covers the subjects as detailed in the syllabus of the General Nursing Council. But, quite apart from nurses in training, a wide variety of professional people—dietitians, welfare workers, almoners—also require a fairly detailed knowledge of hygiene, and this book can be highly commended to them. The writing is good, so that it is easily read, and where necessary the text has been amplified by good line illustrations. Any doctor who gives a series of lectures on hygiene or dietetics will find this a useful volume. It will guide him on how to arrange his course and on what is required in it.

THOMAS ANDERSON.

E.N.T. EXAMINATION

Diseases of the Ear, Nose, and Throat: A Textbook of Clinical and Laboratory Procedures. By Georges Portmann, M.D. Translated by F. Montreuil, M.D., and J. G. Waltner, M.D. (Pp. 728; 666 figures. £7 10s.) London: Baillière, Tindall and Cox. 1951.

This textbook of clinical and laboratory procedures is founded on the author's teaching methods formed after many years' experience. It is confined to the anatomy, physiology, and clinical examination of the upper respiratory tract. The examination of the patient is in all sections described under two headings—"indirect" and "direct"—and the author emphasizes the importance of a searching inquiry into the history, the examiner considering himself a physician rather than a specialist. The author's account of direct examination gives a detailed description of all the possible methods, some of historic interest only and some of doubtful value—for example, transillumination of the mastoid cells by a small lamp in the external meatus—and the student has little guide to their relative importance. All the anatomy is admirable and profusely illustrated with excellent photographs and diagrams.

There are six main sections: ear; nose; mouth and pharynx; larynx, trachea, and bronchi; oesophagus; and a last one, on laboratory methods, not found in English textbooks. There are also full descriptions of the way to take *x*-ray pictures—left to the experts in this country. The section on the ear is particularly detailed, with many photographs to show the canals. The descriptions of caloric, rotation, and electrical testing of the function of the labyrinth are very exact, particularly that of rotation, and pictures show how to test each individual canal. The account of caloric testing includes a description of Hallpike's and Kobrak's methods. It is of interest that Haslinger's instruments for examination of the larynx and bronchi are those commonly used, though Chevalier Jackson's tubes are described.

It is rare to see such a galaxy of admirably reproduced illustrations in any textbook, and the student or indeed the specialist would by their study be able to carry out any test or examination even though he had never seen them applied to a patient.

W. M. MOLLISON.

METHOD IN MEDICINE

De la Méthode en Médecine. By Professor René Cruchet. Second edition. (Pp. 248. No price.) Paris: Presses Universitaires de France. 1951.

This book is the second edition of a volume which was first published in 1942. It was written when France was under German occupation and the author, no longer young, was suffering from privation and unhappiness, written indeed largely to withdraw his mind from so painful a situation. It is one of a series of publications on the logic and philosophy of the sciences, and attempts to deduce what may be called the laws of medicine. It therefore has a close affinity to Dr. Clark-Kennedy's treatise on medicine, though it differs from that book in a more historical approach. The author begins by discussing the spirit of observation in medicine and the definition of diseases. He then discusses in a general way the physical signs of disease, their evolution, the pathological basis, and the aetiology. Finally, there are sections on diagnosis, prognosis, and treatment.

Professor Cruchet is a distinguished neurologist, and like most neurologists he is imbued with a belief in the paramount importance of bedside observation and in the value of direct reasoning from physical signs. In the definition of disease the characteristic grouping of signs and symptoms is more important than the specific cause. To the non-neurologist physical signs no longer have the same appeal, because few other tissues give such specific responses as the nervous system, and those who regard medicine as a branch of applied science or sociology may feel that a preoccupation with signs and symptoms is likely to confine attention to the surface of things. Nevertheless it is good to be reminded that medicine should have a logic and a philosophy. The book is simply produced and written in a clear and easily comprehensible French style.

L. J. WITTS.

APPLIED PHYSIOLOGY

Lehrbuch der speziellen Pathologischen Physiologie. Edited by Ludwig Heilmeyer. Eighth edition, revised. (Pp. 606; 107 illustrations. M. 24.) Jena: Verlag von Gustav Fischer. 1951.

It is surprising that applied physiology has not become independent like anatomy, pure physiology, and morbid anatomy. The subject is of great and growing importance, but is taught by too many experts to be seen as a whole. Applied physiology courses for medical students deal with only a fraction of the subject, most of it being taught by clinicians and pathologists under such names as functional pathology, pathological chemistry, or just plain medicine and surgery. Because of this fragmented teaching, the full range of applied physiology can be seen only in textbooks.

Heilmeyer's *Lehrbuch* has the same object as "Best and Taylor," but is only about half its size. The theme of the book is that applied physiology is a logical development of the work of Wunderlich, Claude Bernard, and Virchow. In contrast to clinical symptomatology, it is concerned to understand the disease process and the mechanism of disordered function. The main divisions of the subject correspond to the physiological systems of the body, but include biochemical divisions that cross system boundaries. Various authorities write on the blood, the respiration, the circulation, the kidneys, the alimentary system, vitamin deficiencies, metabolism, and the vegetative nervous system and ductless glands. The work is up to date and gives long bibliographies; these are virtually restricted to textbooks and monographs, most of them German. The analytical table of contents and the index are of the customary Teutonic excellence, but the text paper and cover are of poor quality—a matter for sympathy rather than censure. The many previous editions show the value of the book to German students and doctors; outside Germany, teachers may find it useful for reference.

RAYMOND WHITEHEAD.

ALLERGY REVIEWED

Progress in Allergy. Volume 3. (*Fortschritte der Allergielehre*.) Edited by Paul Kallos. (Pp. 572; 82 figures. Swiss francs 68.65.) Basle: S. Karger. 1952.

The editor of this book, Paul Kallos, writes a general introduction and an excellent brief review of the use of ergot derivatives in migraine. The dozen contributors are allowed complete freedom of expression, which is obviously a wise policy but leads to some overlapping and contradiction.

General reviews are given by Dr. M. Murray Peshkin of allergy in children, Dr. Leon Unger of bronchial asthma, Dr. Joseph Harkavy of cardiovascular allergy, and Dr. Ethan Brown of drug allergy. Dr. Albert Rowe reviews bronchial asthma due to food allergy, and Dr. David Harley the infective factor in asthma; he expresses strongly his belief in the value of bacterial vaccines made by the pathogen-selective-culture method. Dr. Arthur Stoll discusses the chemistry of the ergot alkaloids, and Dr. E. Rothlin and Dr. R. Bircher contribute an article on the actions of these alkaloids in allergic states. The volume ends by a logical and model article by Dr. J. F. Ackroyd on "sedormid" purpura. Surprisingly enough in a book dated 1952, there is but scanty mention of A.C.T.H. and cortisone in relation to allergic conditions. To sum up, this volume, like previous ones in this series, gives an excellent account of their contributors' present views and practice, and will therefore be read with benefit by all interested in the subject of allergy.

C. J. C. BRITTON.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY AUGUST 16 1952

TREATMENT OF CORONARY THROMBOSIS

Following the report of the committee of the American Heart Association, which recommended the use of anticoagulant drugs in the treatment of coronary thrombosis,[1] Tullock and Gilchrist[2] and many others confirmed that the mortality and incidence of thrombo-embolic complications could be reduced with heparin and dicoumarol. In this issue on page 351 Dr. Rae Gilchrist gives his latest results, using in some cases "tromexan" instead of dicoumarol. In his control group the mortality was 43%, compared with 21% in the group receiving anticoagulants. The expected fall in the incidence of thrombo-embolic complications and in deaths from this cause occurred, but more surprising was the reduction in mortality from 15% to 4% in patients showing shock. In this last group it is difficult to attribute the improvement to the anticoagulant action of the drugs, and it may well be that other less well understood actions of these drugs were responsible. Graham and his colleagues[3] in the course of an investigation into the influence of heparin on lipoprotein metabolism found that 55 of 59 patients with angina pectoris had marked relief of symptoms when given injections of heparin once or twice a week, although the pain returned when inert injections were substituted. These results with small intermittent doses cannot be due to either the vasodilator or the antithrombotic action of heparin. There seems to be no doubt that in severely ill patients the anticoagulants have an important place in treatment, but it is more difficult to justify their routine use in all cases of coronary thrombosis.

Russek and Zohman[4] in a series of 1,047 cases treated conservatively separated them into "good risk" and "bad risk" groups on the basis of information available on the day of admission to hospital. Their serious prognostic signs were a history of previous infarction, intractable pain, severe or persistent shock, cardiac enlargement, gallop rhythm, heart failure, and arrhythmias, and if none of these factors were present the mortality was only 3.1%, compared with 60% in the group showing one or more of these signs. Their results might well serve as a basis for the selection of cases for anticoagulant treatment, since the risks of treatment with inadequate laboratory control are considerable, whereas with conservative treatment, frequently carried out in the patient's own home, recovery can be expected in the majority of good-risk cases.

Morris, Heady, and Bailey,[5] in their study of coronary heart disease in medical practitioners, showed that most deaths from coronary thrombosis occurred during the first week and that the time of greatest need for therapy was in the first few days of the first clinical attack. The chief causes of death during this period are shock and congestive heart failure, and Gilchrist emphasizes the importance of early treatment of heart failure. Although the circulatory changes during cardiogenic shock are still obscure, the hypotension would seem to be due to failure of the viable myocardium,[6] and in a severe case he advises the use of digoxin as a cardiac stimulant in spite of the largely theoretical objections to its use in the presence of a recent infarct. The evil effects of prolonged hypotension, which can itself cause ischaemic changes in the myocardium, are generally recognized, but unfortunately there is at present no reliable way of raising the blood pressure. The use of pressor drugs is still in the experimental stage, and the results of transfusion, either intravenous or intra-arterial, have been discouraging. Research into the causation and treatment of cardiogenic shock might well lead to a reduction in the mortality from coronary thrombosis during the dangerous first week comparable with that which the anticoagulants have achieved through decreasing the incidence of thrombo-embolism.

[1] *Amer. Heart J.*, 1948, **36**, 801.
[2] *British Medical Journal*, 1950, **2**, 965.
[3] *Circulation (N.Y.)*, 1951, **4**, 666.
[4] *Amer. Heart J.*, 1952, **43**, 871.
[5] *British Medical Journal*, 1952, **1**, 503.
[6] *Circulation (N.Y.)*, 1952, **5**, 609.

EPIDEMIOLOGY OF POLIOMYELITIS

Acute poliomyelitis is well known as a disease of warm dry weather, and it can have surprised nobody that the recent spell of unusually hot weather has been followed by a rise in the notifications of this disease. Since the first great epidemic in this country in the hot summer of 1947 the seasonal rise in notifications has begun with the hot weather. Generally the return of cooler weather has seen a considerable decline in incidence, although there has been a tendency for the tail-end of the epidemic to continue well into the colder season; the epidemic of 1949 was not completed until the beginning of the following year. Poliomyelitis incidence was comparatively low in 1948, which was not a particularly warm year.

The striking seasonal variation in incidence that characterizes poliomyelitis in temperate climates has

attracted the attention of many workers, who have seen in it a possible clue to some of the riddles of the epidemiology of the disease. The obvious possibility that meteorological conditions might affect the ease of transmission of infection from one person to another or the survival of the virus during transfer is but one aspect of this problem. Other secondary changes take place as a result of the warm weather. There is a change in our whole mode of life and in the ventilation of our dwellings; flies and other insects increase in numbers; there is an increase in the incidence of intestinal infections, and epidemics of "summer throat" occur. We do not know if these and many other secondary effects of the warm weather are of any importance in the spread of the disease.

Attempts have been made to correlate incidence with temperature and humidity, and, although the association has frequently been close, anomalies that defy explanation are not uncommon. Snow,[1] for instance, has recently described the meteorological findings during epidemics of poliomyelitis in Australian cities. During the Sydney epidemic of 1950–1 and that in Adelaide in 1949–50 there was a close correlation between poliomyelitis incidence, rising temperature, and rising saturation deficit, this being the usual finding in poliomyelitis epidemics. But he records that the epidemic in Perth in 1948 took place in weather conditions which were precisely the reverse of those found in subsequent years in Sydney and Adelaide, the peak of the epidemic occurring in July, when temperature and saturation deficit were at their lowest. Moreover, the disease can spread during the Arctic winter, giving rise to outbreaks of exceptional severity and high attack rate.[2] In spite of such exceptions it nevertheless remains true that poliomyelitis epidemics occur most frequently in hot dry weather.

Attention has been drawn to the fact that the time of year at which poliomyelitis reaches its highest incidence is also the time when enteric fever and food-poisoning are most prevalent, and this fact, linked with the knowledge that poliomyelitis virus is excreted in the stools, has been used as an argument in favour of a similarity in the mode of spread of all these diseases. But the analogy is not complete. It may be assumed that one of the factors making for increased incidence of the intestinal infections is the greater ease with which bacteria can multiply outside the body in the warm weather. Salmonella organisms may multiply happily in food at room temperature on a summer afternoon, but viruses have shown the greatest reluctance to multiply outside the living cell. There is no convincing evidence that poliomyelitis has been disseminated by infected food or milk, although the possibility that this type of spread might occur cannot be dismissed. Similarly, evidence is lacking that the virus has been transmitted by public water supplies, and there are good reasons for believing that chlorination will destroy any virus that may be present.[3] The epidemiological evidence points firmly to personal contact as the most important factor in the spread of the disease. In one American investigation the virus was obtained from the stools of 54 of 101 contacts, but from only 6 of 55 non-contacts living in the same block.[4]

How then can the seasonal incidence of poliomyelitis be related to transmission by personal contact? The hypothesis of Armstrong[5,6] offers at least a possible explanation. He suggests that when cold dry air is inspired the secretions of the nasopharynx are increased and act as a protective barrier between the virus and the nasopharyngeal cells. In the warmer weather the secretions are reduced, and the conditions are more suitable for invasion by the virus. Support for this idea is provided by figures showing a close correlation between poliomyelitis incidence and the relative humidity of the air adjusted to the temperature of inspired air, and also by experimental evidence of the protective effect of mucin in virus infections.

Meanwhile Logan[7] has described the age, sex, and geographical distribution of cases and deaths in recent epidemics in Britain. He shows that the association of incidence with population density differs with age, the attack rate under the age of 5 years increasing with urbanization, the reverse being the case at older ages. When the incidence from 1946 to 1950 is examined in the Registrar-General's Standard Regions it is found that the median age of notification in a region varies inversely with the infant mortality rate, which suggests the possibility that favourable environmental circumstances may postpone the age of attack. Among other information in this interesting study is a table giving the age in months of 291 cases under 1 year of age notified during 1950; 28 of these babies were aged under 3 months.

Although it would be most desirable to know more about the method of spread of poliomyelitis virus and the relative importance of faeces and nasopharyngeal secretions in the transfer of infection, the continued prevalence of Sonne dysentery and measles serves as a reminder that increased knowledge of the method of transmission of poliomyelitis would not necessarily lead to effective control measures. One of the out-

[1] *Med. J. Aust.*, 1952, **2**, 17.
[2] Peart, A. F. W., *Canad. J. publ. Hlth*, 1949, **40**, 405.
[3] Maxcy, K., *J. Amer. Waterworks Ass.*, 1949, **41**, 696.
[4] Casey, A. E., *et al.*, *Amer. J. publ. Hlth*, 1950, **40**, 1241.
[5] Ibid., 1950, **40**, 1296.
[6] Ibid., 1951, **41**, 1231.
[7] *Monthly Bull. Minist. Hlth, Lond.*, 1952, **11**, 147.
[8] *Amer. J. Hyg.*, 1952, **55**, 108.
[9] *Ann. intern. Med.*, 1952, **37**, 1.

standing facts about the epidemiology of poliomyelitis is that although each epidemic brings its personal tragedies the virus is a mercifully benign parasite for the majority of those infected, giving rise to little or no disturbance. Any conditions that may alter the vulnerability of the nervous system are therefore worth investigation, and the study of the possible role of trauma, throat operations, inoculations, and excessive physical activity is of the greatest importance.

It is possible that when a solution of the problem of poliomyelitis is found it will take the form of active immunization. This possibility has been taken a stage further by the work of Koprowski, Jervis, and Norton[8] in feeding a vaccine by mouth to human beings. Gear[9] has recently reviewed the work on immunization, and concludes that "the situation in poliomyelitis is brighter now than it has ever been." But the work is still in its early stages, and the difficulties in carrying out research of this type are formidable. It would be wise not to be too hopeful of early success.

TUBERCULOUS MENINGITIS

Two diseases, once uniformly fatal, are now sometimes curable by courses of treatment more arduous than anything known in therapeutics before the advent of antibiotics. The treatment of bacterial endocarditis is an ordeal for the patient: that of tuberculous meningitis a worse one for patient, nurse, and doctor, whatever the system employed. That recommended by Dr. A. R. Somner, who describes his experience with 26 cases on page 356, is daily intramuscular injection of streptomycin for at least six months, together with intrathecal injections on about three-quarters of the days in this period. It seems clear from his analysis of these cases, among which the earlier ones had shorter initial periods of treatment, that this prolonged course affords the best chance of success: it is a striking fact that among patients who had as many as 144 intrathecal injections none has subsequently died. In 11 patients the development of a spinal block, which was often temporary and is regarded as in part an effect of streptomycin on the meninges, necessitated resort to cisternal puncture: this was performed in one patient no less than 46 times. The time occupied in skilled attention to such patients must far exceed that called for in any other disease, and anyone embarking on the treatment of a case of tuberculous meningitis must recognize at the outset what is called for, and should refer the case forthwith to a special centre unless every facility for the treatment is available.

Although 14 of these 26 patients have survived, four are totally deaf, and five others have various degrees of impairment of hearing. It is generally agreed that this complication is caused by the drug and not by the disease. It would be interesting to know the age distribution of degrees of deafness in this series, because the younger patients must have received a proportionately higher dose in relation to body weight: the intramuscular dosage varied only between 0.5 and 1 g. and the intrathecal between 50 and 100 mg., whereas age varied from 1 to 27 years. It has been a common practice to give half the adult dose to infants, despite a much greater difference in body weight, and it would be worth while to inquire whether this accounts for the better therapeutic results commonly obtained in the early age group, or whether, on the other hand, a dose calculated more nearly according to body weight might not be adequate and perhaps preferable.

The other point of interest in connexion with deafness in this series is that it resulted almost exclusively from the use of dihydrostreptomycin: all three recovered patients treated with this drug only are totally deaf, and of five others, part of whose treatment was conducted with it and part with streptomycin, four have hearing impairment. Deafness produced by this form of the drug is peculiarly insidious: it may even develop some time after treatment has stopped. It is almost incredible now that dihydrostreptomycin should ever have been acclaimed as free from the toxicity of streptomycin, when in fact its only virtue at that time was greater freedom from impurities causing minor toxic reactions. It is interesting to recollect that this *Journal* was once taken to task under banner headlines by a Sunday newspaper for being "two hydrogen atoms behind" in a leading article[1] counselling some caution in the use of streptomycin at a time when there was a strong tendency to employ it promiscuously. It has now proved that the form of the drug which we were accused of having ignored is more dangerous than the original. We may add that the policy of caution recommended in this offending leading article coincides with that of the best-informed opinion at the present day: indeed, it is the view of leading authorities in the U.S.A. that, owing both to the possibility of toxic effects and to the fact that so many strains of most pathogenic bacteria are liable to be resistant to it, streptomycin should be reserved exclusively for the treatment of tuberculosis.

Since specific treatment became possible, it has been of much greater importance to be able to verify the diagnosis certainly and immediately; hence the changes in the cerebrospinal fluid have been intensively restudied. Somner confirms the conclusion reached by others that a diminished sugar content is the most constant and reliable positive sign. This estimation also furnishes a guide to prognosis, and to the length of treatment necessary: he concludes that treatment should not be stopped, however favourable other features of the case may appear to be, until the sugar content has returned to 50 mg. per 100 ml. A fall in the chloride content is also an almost invariable diagnostic finding; this value is said to return to normal during treatment earlier than the sugar, but to be subject to inexplicable minor variations (presumably these were not due to the use of wet apparatus for puncture). The protein and cellular content are of less diagnostic value, since they may be similarly changed in other conditions, and of very little prognostic value, because intrathecal streptomycin treatment itself contributes to and perpetuates the

[1] *British Medical Journal*, 1949, 2, 1098.

abnormalities. Diagnosis is also discussed by Dr. R. W. S. Harvey on page 360 on the basis of laboratory findings in 150 cases. He agrees in laying stress on a diminished sugar content, which he found to be of sufficient degree to be distinguished by a simple qualitative test. This paper is concerned chiefly with methods for demonstrating tubercle bacilli, and it is interesting that as many positive results (103, or 69%) were obtained by direct film in the first specimens received as by either cultivation or animal inoculation. How much more useful a reliable immediate finding is than one involving a delay of three weeks needs no emphasis. The technique by which this was achieved consisted of centrifugation in a special home-made tube tapering to a fine point in which the deposit was concentrated, and the transfer of this deposit by means of a fine capillary pipette to a slide on which it was placed in minute drops. The area covered by each of these was so small that the whole of it could be searched microscopically in a short time, and in fact bacilli were found in less than 10 minutes, and often in less than five, in the majority of 71 successful searches actually timed.

MEDICAL LABORATORY TECHNOLOGY

The opening of the triennial conference of the Institute of Medical Laboratory Technology at the London School of Hygiene and Tropical Medicine on July 28 by Miss M. P. Hornsby-Smith, Parliamentary Secretary to the Ministry of Health, was followed by four days of scientific meetings, demonstrations, and visits to places of scientific interest. It was attended by about 200 members from the provinces or abroad as well as by large numbers of those resident in London. The Institute, which originated as the Pathological and Bacteriological Laboratory Assistants' Association in 1912, has now a far larger membership than ever before. One reason for this is the expansion of pathological services throughout the country, which began during the war and has continued under the National Health Service, with the result that the total number of technicians employed in hospital laboratories has risen considerably. A second reason is the recognition, now almost universal, of the advantages which membership of the Institute confers, more particularly the advantage of having obtained its qualifications. The original Association became an examining body in 1921, with the full support of the Pathological Society of Great Britain and Ireland, whose members, together with an equal number of senior members of the Association, acted as examiners. This system has continued to the present day, although the final examination can now be taken in a greater number of branches of the subject. There is also a general intermediate examination, and a requirement of five years' training in a recognized laboratory before the final can be taken. A higher qualification, the Fellowship of the Institute, can be obtained by passing the final in a second subject, or by thesis. These stages thus represent three grades of attainment, and it is upon reaching them that appointment or promotion to posts of different degrees of seniority now largely depends. The requirement that a candidate for a post shall possess a qualification of the Institute has been usual in the past, but the possession of it will assume even greater importance in the future if the recommendations of the Cope Committee are implemented. The report of this Committee proposes a system of State registration for several classes of "medical auxiliary," including technicians in pathological laboratories, comparable to that for the medical and nursing professions. If this comes about, admission to the register will depend on obtaining the Institute's qualifications. In coping with its rapidly expanding duties, of which some idea may be gained from the fact that there were over 800 candidates for the final examinations this summer, the Institute requires and deserves the support of everyone in a responsible position in the profession of pathology.

METHAEMOGLOBINAEMIA

Before 1945 few cases of methaemoglobinaemia had been reported, and the condition was regarded as excessively rare. Since that time the total number of cases has approached 100, as Dr. A. Codounis describes elsewhere in this issue, and a few of these have been studied in some detail by laboratory methods.[1 2] The laboratory studies have shown that normal human erythrocytes are able to convert about 5% of their total pigment from methaemoglobin (MHb) to haemoglobin in an hour. This reduction is achieved by enzymes and coenzymes within the cell, which oxidize and again reduce one another in sequence, the mechanism involving coenzyme I (containing nicotinamide) and diaphorase I (containing riboflavin and a protein). An additional possible pathway through coenzyme II and diaphorase II (the same riboflavin compound, but a different protein) does not appear to be active unless a reversibly oxidizable dyestuff such as methylene blue is added to function as a carrier between diaphorase II and MHb. Reduced diaphorase II cannot reduce MHb, but it can reduce the dyestuff, which can then reduce MHb, becoming itself reoxidized in the process.

It is likely that small amounts of MHb are being formed continuously in the erythrocytes of normal persons by auto-oxidation of haemoglobin,[1] but, because of the active reducing mechanism, only traces of MHb are found in the circulating blood. Erythrocytes from cases of familial methaemoglobinaemia, however, are deficient in diaphorase I activity; they do not reduce MHb at a significant rate, and accordingly MHb accumulates in them. The level of MHb does not continue to mount indefinitely, because, as it rises, the rate of direct chemical reduction by substances such as ascorbic acid increases also, and an equilibrium is established when from 10 to 40% of the total pigment has been oxidized. Quite a different state of affairs exists in toxic methaemoglobinaemia (as, for example, in Dr. W. A. B. Campbell's case on page 371), where the normal reducing mechanisms are intact but are overwhelmed by the large amounts of MHb produced by the toxic agent. In one interesting case of toxic methaemoglobinaemia studied by Fishberg[4] the toxic

[1] Bancroft, H., *et al.*, *Clin. Sci.*, 1945, **5**, 145.
[2] Gibson, Q. H., *Biochem. J.*, 1948, **42**, 13.
[3] Brooks, L., *Proc. roy. Soc. B.*, 1931, **109**, 35.
[4] *J. biol. Chem.*, 1948, **172**, 155.

compound was benzoquinone acetic acid, presumably formed from tyrosine and so independent of the ingestion of drugs.

The recognition of distinct varieties of methaemoglobinaemia is of something more than academic interest, since two effective means of therapy are available in ascorbic acid and methylene blue. In familial methaemoglobinaemia it seems likely that ascorbic acid acts as a simple chemical reducing agent, displacing the equilibrium between haemoglobin and MHb in favour of haemoglobin. With the concentration of ascorbic acid which can be obtained in the blood the rate of reduction of MHb is very low, and some weeks are required before the full effect is obtained. Unless ascorbic acid reacts directly with the MHb-forming drug, it follows that it can have no influence on the course of a toxic methaemoglobinaemia. In Fishberg's singular case, indeed, ascorbic acid caused the immediate disappearance of benzoquinone acetic acid from the urine, and MHb disappeared from the blood within 24 hours; but this is an isolated instance. It would seem, then, that in toxic methaemoglobinaemia, if active treatment is required, methylene blue should be given, since it acts rapidly and effectively through the diaphorase II mechanism.

Detailed biochemical studies of the enzymes in the erythrocyte have been made on only seven cases of the familial form, and it is by no means impossible that forms of methaemoglobinaemia other than those so far described may exist. It is most desirable that those who have the good fortune to encounter further cases should not rest content with the spectroscopic demonstration of MHb in the blood, but should seek biochemical assistance in examining the enzyme systems within the red cells.

RESTRICTIONS ON HYPNOTISM

The Hypnotism Act, which comes into force on April 1 next year, makes it illegal to hypnotize anyone under 21 except for purposes of scientific research or medical therapy. It also gives local authorities power to control exhibitions of hypnotism in all places licensed for public entertainment, and makes their permission obligatory for any other public show, even if admission is free. The medical sponsors of the Bill in Parliament originally wanted to ban mesmerism as an entertainment completely, but this seems to have been too far ahead of public opinion, which apparently prefers to leave to local feeling the decision whether the local music hall or charity garden fête may include a hypnotist among its attractions. Since the Act does not apply to Northern Ireland, and the maximum fine for its contravention is in any case only £50—which is small in relation to theatrical earnings—the stage entertainer may be somewhat restricted after next All Fools' Day, but he is unlikely to be put out of business.

The B.M.A.'s Psychological Medicine Group Committee recently[1] reaffirmed its view that the hypnotic state should be induced only by a medical practitioner and only for therapeutic purposes. However, it has to be admitted that the evidence that hypnotism in other circumstances can do positive harm is at present scanty, and the subject remains more controversial than corneal grafting or the fitting of fireguards, both the subject of other successful private members' Bills in the parliamentary session just ended. The Government was doubtless anxious not to limit more than necessary the choice of an adult to do what he pleases, and has therefore decided there is some case for leaving to the individual the choice of being publicly hypnotized. The medical men who introduced this new legislation may be congratulated on what they managed to achieve, and the effects of the new Act will be watched with interest when it comes into force next year.

[1] *British Medical Journal Supplement*, May 31, p. 258.

NURSING AT 18

One of the original statutory rules laid down by the General Nursing Council some 30 years ago required a nurse to have attained the age of 21 before qualification. At that time most general hospitals preferred, and were able to select, young women of 20 years and over for training. The rule may have been designed to ensure that younger girls, who often undertook sick children's or fever training before entering general hospitals, had reached 21 years before becoming State registered. This rule has remained unaltered in spite of the increasing demand for nurses and the decreasing age of the entrants. Recently the General Nursing Council has added another rule. From August 1, 1952, the minimum age of entry for nurse training is fixed at 18 years.

How is this going to affect the recruitment of student nurses? For some years it has been the practice of many hospitals to admit students at 17½ or even younger. In view of the problems likely to be created by the new regulation *The Times*[1] has asked for representative opinions from a cross-section of matrons and hospital administrators. It collected some differing views. There appears to be agreement that the age of entry for general training should be 18 years, but opinions vary over the same requirement for entrants to hospitals for sick children. Some matrons are experiencing a shortage of eligible applicants. The larger teaching hospitals are least likely to be affected. Some critics say that widening the gap between school leaving and entry to hospital may cause more loss to other occupations.

The nursing profession is well aware of its problems and responsibilities. Are the training and status of nurses likely to be improved by the requirement of a minimum age of entry? Can a statutory body decide the age when young people are mature and stable enough to undertake the arduous duties of modern nursing? Would there be less wastage if nurses were older when they entered? This rule aims at improvement. If the profession is to maintain its reputation for skill and competence, any move to exclude the too young entrant should be welcomed and given serious trial. Fortunately the regulation has a clause which empowers the General Nursing Council to use its discretion to waive the requirement "where the strict application would be likely to affect the hospital services prejudicially."

[1] July 28, p. 7.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE SURGICAL RELIEF OF PAIN*

BY

LAMBERT ROGERS, M.D., F.R.C.S.

Professor of Surgery, University of Wales; Surgeon, United Cardiff Hospitals; Consultant in Neurosurgery to the Royal Navy

Remembering that pain is but a symptom and its biological purpose for the most part protective, we must seek to allay its cause. This may, however, be unknown or imperfectly understood, as in trigeminal neuralgia, or well known but no longer within the range of effective local treatment, as in myocardial ischaemia or inoperable malignant disease. In such cases our efforts must be wholly directed to relieving the symptom of pain. Surgical methods for its relief will usually be considered only after lesser measures in the form of anodynes have failed or for any reason are no longer advisable.

Pain may be relieved or abolished by:

(1) Removing its source, thereby eliminating the noxious impulses which are giving rise to it—for example, the pain of appendicitis by appendicectomy, of gallstones or renal colic by getting rid of the offending calculi.

(2) The administration of anaesthetics—for example, in tetanic spasms—or analgesic drugs—for example, morphine in cardiac infarction.

(3) The interruption of the pathways of the painful impulses in order to abolish or modify their effects on the sensorium, either before they reach it or in the brain itself, by operations such as neurotomy, rhizotomy, chordotomy, medullary or mesencephalic tractotomy, or frontal lobotomy.

(4) Increasing the blood supply to the painful part so as to reduce or abolish the pain of ischaemia.

We should also remember that irradiation will sometimes diminish the pain of malignant disease, though for a time it may make the patient feel very ill.

To employ surgical measures for the relief of pain in those cases in which it is not possible or feasible to attack the lesion which is its source, it is necessary to know the course taken by the painful impulses in the nervous system and those sites where they may be interrupted, either by sectioning or coagulation or by the injection of chemical substances such as procaine, alcohol, or phenol.

The Course of Pain Impulses

Pain impulses enter the posterior root ganglia of the spinal cord from spinal nerves and are passed into the cord by way of the central processes of these ganglia. In the substantia gelatinosa of Rolando they ramify in relation to cell bodies of secondary neurones, the axons of which cross in the anterior commissure over the course of a few segments and as a crossed tract (spino-thalamic) pass upwards in an antero-lateral position in the cord. After traversing the medulla and the brain stem these fibres end in cells in nuclei in the thalamus, whence they are connected by other neurones with the sensori-motor, orbito-frontal, and probably other parts of the cerebral cortex. Pain impulses also traverse certain parts of the sympathetic nervous system.

The passage of pain impulses may thus be interrupted at any of the following sites: (1) the nerves conveying them; (2) the posterior spinal root or roots; (3) the pain tract in the spinal cord; (4) the pain tract in the medulla; (5) the pain tract in the brain stem; or (6) the cortico-thalamic fibres in the frontal lobe.

*A Refresher Course article entitled "The Medical Relief of Pain," by Professor E. J. Wayne, was printed in the *Journal* of September 29, 1951 (p. 787). The present article, by Professor Lambert Rogers, is based on the John Tate Memorial Lecture delivered to the Middlesex Medical Society on July 1, 1952.

What Surgery Can Offer

Division of Nerves.—This is not often performed. In Buerger's disease the nerves to the foot have been severed in the hope of relieving the pain, but the operation is rarely effective. In certain cases of supraorbital neuralgia relief is sometimes obtained if the nerve is injected or divided as it leaves the supraorbital notch or foramen.

Posterior Root Section (Foerster's Operation).—This is effective in cases of localized root pain such as may be due to spinal arachnoiditis. It is not feasible to denervate completely the sensory part of a limb, for a painful condition in it, by dividing all the posterior roots of the plexus by which it is innervated. If this is done the limb becomes useless, since knowledge of its presence and position is lost to the patient. This operation of posterior rhizotomy, therefore, has only limited use, with the great exception, however, of the trigeminal nerve in facial neuralgia.

Posterior-root section of the Gasserian (trigeminal) ganglion is a most satisfactory operation for relieving the intense pain of major trigeminal neuralgia. The sensory (posterior) root is divided proximal to the ganglion, either by approaching it, as is the usual practice, by a temporal route or else through the posterior fossa of the skull. The division of the trigeminal root may be partial and selective, so that in cases in which there is no pain in the distribution of the ophthalmic division the medial part of the root, which contains the ophthalmic fibres, may be left intact and sensation thereby preserved in the cornea.

When divided, a sensory root, in contradistinction to a dendron—for example, a peripheral nerve or peripheral part of the trigeminal—does not regenerate, so that such divisions are permanent and the relief of pain is permanent.

Chordotomy.—The pain tract in the spinal cord may be divided by a cross-section of the antero-lateral area of that part of the spinal cord in which it lies or by a longitudinal section designed to cut the crossing fibres in the commissure. The latter operation is rarely practised, and antero-lateral chordotomy, performed a few segments higher than the level below which the pain is to be abolished, is the operation of choice (Figs. 1 and 2). It is employed for conditions such as inoperable malignant disease. The result of the

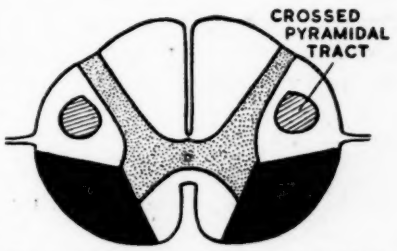


FIG. 1.—Chordotomy. The section (black area) avoids the important crossed pyramidal motor tract.

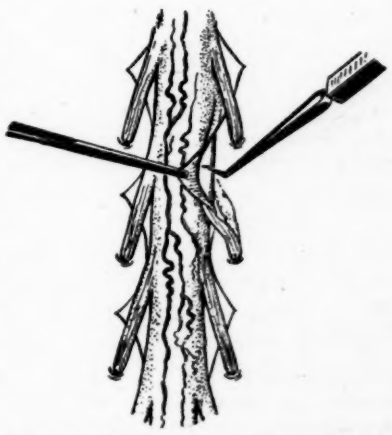


FIG. 2.—Chordotomy. The cord is rotated by gentle traction on a slip of the dentate ligament and the section made in front of the plane of attachment of the ligament.

operation is to abolish pain and temperature sensations on the opposite side of the body below the section, light touch and the proprioceptive sensations being retained. There is a tendency for the level of analgesia to "fade," and recently emphasis has been laid on the necessity to be more radical in the section than had previously been thought to be necessary. The site and distribution of the pain determines whether the section is to be made on the opposite side of the cord alone or whether the operation is to be a bilateral one.

Dorsal Chordotomy for Painful Phantom Limbs.—In patients over 4 years of age amputation of a limb produces a phantom hand or foot which lasts for a varying time and then fades and disappears. In some cases (probably about 7%) pain, which may be intense, persists in the phantom member, which seems to the patient to be in a distorted posture, the pain being described as cramping, squeezing, or twisting in character. Various operations have been performed in an attempt to abolish this pain—for example, sympathectomy, rhizotomy, antero-lateral chordotomy, and even excision of part of the parietal cerebral cortex—without much success in most cases. A recent operation which has given relief and appears more promising is the division at an appropriate level in the spinal cord of the dorsal columns (tracts of Goll and Burdach) concerned with posture.

Medullary Tractotomy.—The incision is made in the brain stem between the origin of the vagal roots and the inferior olive; the indications are the same as for chordotomy, with the addition of trigeminal neuralgia, since the descending root of the trigeminal nerve can be divided at this level (Fig. 3). This is not the most popular operation for trigeminal neuralgia, however. The operation may give relief in cases of malignant disease of the apex of the lung which has infiltrated the brachial plexus, a condition in which pain may be persistent and severe.

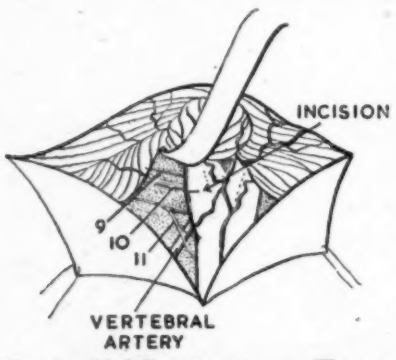


FIG. 3.—Medullary tractotomy. The section is made between the origin of the vagal roots and the inferior olive.

Mesencephalic Tractotomy. — At the level of the inferior colliculus the spino-thalamic tract, which has been joined by the trigeminal fibres, is superficial and its division produces hemi-analgesia. Queer sensations (dysaesthesia) are reported, however, as occurring later in some cases, and as sensory disturbances of this type do not follow more caudal sections—for example, chordotomy and medullary tractotomy—the mesencephalic operation is not often performed.

Prefrontal Leucotomy.—Ablation or section of the frontal lobes lessens or abolishes stress and thereby the intensity of pain, but produces changes in personality. The operation does not abolish the perception of pain but relieves the suffering from it so that the patient may regard it lightly or even humorously. This operation raises the question whether the surgeon has the moral right to produce irreversible changes in those structures which constitute the matrix of the mind and so alter the personality of a fellow being, but this is perhaps less debatable if the patient suffers from inoperable malignant disease. Recent work, however, has made this question less significant by showing that pain may be relieved by far less extensive operations on the frontal lobes than their removal or transection by the usual type of lobotomy. The section need only be confined to the medial ventral quadrant of the lobe, with the result that the appropriate cortical connexions of the thalamus are severed, while the lateral parts of the lobe which constitute the neopallium and are primarily concerned with learning, memory, and intellectual functions are left intact. Realization that the area in which interruption is essential for the relief of pain is thus restricted anatomically is an important advance, and still further progress has been made by the use of an insulated needle-electrode to coagulate a barrier of cerebral tissue in the area concerned* instead of dividing it through a cortical incision. Whether this limited orbito-frontal leucotomy relieves pain by relieving anxiety and tension or by severing visceral afferent cortico-thalamic fibres is disputable, but the fact that pain can be so relieved is definite. Pain which is associated with undue mental stress or other emotional factors is the type for the relief of which these operations on the frontal part of the brain are particularly effective.

Sympathectomy.—In painful conditions due to ischaemia, in which improvement in blood supply by relaxing the arterioles can be brought about by sympathectomy, this operation may be indicated. Thus in early cases of thromboangiitis and of arteriosclerosis in which there is associated vasospasm causing claudication, lumbar ganglionectomy may give welcome relief. In cases of causalgia after peripheral nerve injury or following amputation—for example, of a digit—sympathectomy may also be palliative. The operation has also been successful in certain cases of dysmenorrhoea, the sympathetic fibres in front of the sacral promontory and constituting the nerve of Latarget or the Frankenhausen plexus being divided (the Cotte operation). Cervicothoracic sympathectomy has also been employed with success in cases of angina pectoris.

Other methods of relieving pain, such as the intrathecal injection of alcohol or radiotherapy in malignant disease, need only be mentioned here. It will be seen that we have ample resources to enable us, when other measures fail or are contraindicated, to relieve pain by surgical methods. For this reason, and also because it is our duty to preserve and not take life, no case can be made for introducing legislation for euthanasia.

> "And that must end us; that must be our cure,—
> To be no more. Sad cure! for who would lose,
> Though full of pain, this intellectual being,
> Those thoughts that wander through eternity."
>
> *Paradise Lost*, Book 2, lines 145–8.

Of the foregoing operations for the relief of pain the most successful and most often practised are root section for trigeminal neuralgia, sympathectomy for vascular insufficiency, and antero-lateral cordotomy for intractable pain in malignant disease.

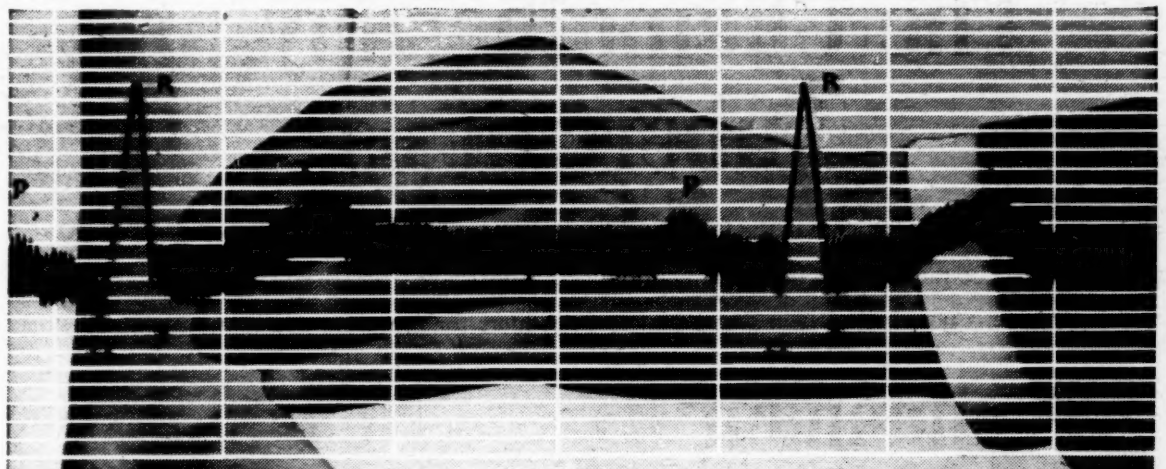
Indications for Surgery

Whether to employ analgesic drugs or surgical methods must be determined by the state of the patient and the condition from which he suffers. The decision will be influenced by his probable length of life, and generally speaking it may be said that if this is likely to be short morphine and its allies are indicated, while if it is likely to be prolonged surgical methods may better be employed.

When pain is purely psychological in type caution is necessary and operations should be avoided. The numbness which follows the analgesia produced by operation in such cases may be as great a source of complaint as the original pain, and as the numbness cannot be relieved the last state of the patient is worse than the first. One type of case which may come into this category is the young adult, usually a woman, with pain in the face. We should hesitate to diagnose true trigeminal neuralgia in patients under 50 who do not have recurrent attacks confined strictly to the field of distribution of one or more branches of the trigeminal nerve.

Finally, let us not forget that the ideal, though not always practicable, treatment of pain by surgical methods is to find the cause and remove it.

*E. G. Grantham, *J. Neurosurg.*, 1951, **8**, 405.



THE CLINICIAN CHOOSES . . . .

In the majority of recent papers on digitalis action, the drug described was Digoxin. Digoxin is selected for clinical research in cardiology because it is a pure glycoside of constant composition, is very rapid in action, and its rate of elimination is slow enough to allow adequate maintenance therapy. Digoxin rarely produces local gastric effects. As in research, so in practice. For accuracy and safety the first choice is . . . .

DIGOXIN

'B. W. & CO.'

BURROUGHS WELLCOME & CO.
(THE WELLCOME FOUNDATION LTD.) **LONDON**

The Chemotherapy of Tuberculosis

Over the past few years research in the field of tuberculosis has produced several valuable chemotherapeutic agents, the most recent being isonicotinic acid hydrazide. ***Neumandin*** Brand isonicotinic acid hydrazide is now included in Boots range of products for the treatment of tuberculosis.

Neumandin Brand

Isonicotinic Acid Hydrazide
Tablets of 50 mg.
Bottles of 100 and 1,000
(*Supplied to hospitals and clinics only*)

Neustab Brand

Thiacetazone
TABLETS FOR ORAL ADMINISTRATION
25 or 50 mg. Bottles of 50, 250 and 1,000
STERILE POWDER FOR LOCAL APPLICATION
Vials of 100 mg. Boxes of 10

P.A.S. Cachets

Each containing 1.5 G. Sodium para-Aminosalicylate. Boxes of 50

Literature and further information available from the Medical Department,
BOOTS PURE DRUG CO. LTD. NOTTINGHAM ENGLAND (S139)

Rx
Sterathal Suspension
Mitte 3iv
Sig. 3ii q.i.d.

for INFANTILE GASTRO-ENTERITIS

Detailed literature and samples available on request.

Sterathal Suspension contains phthalyl sulphacetamide (10.5%) — a new sulphonamide of low toxicity which exerts maximum chemotherapeutic activity in both the lumen and wall of the intestinal tract. Systemic absorption is negligible and also included is Pectin (2.5%), a detoxicant in the large bowel and Kaolin (10%), a protective and adsorbent in the small intestine.

Although the Suspension contains no sugar, it is palatable and readily acceptable by both children and adults alike in the treatment of specific and non-specific diarrhœas, gastro-enteritis and the so-called "summer diarrhœa" which is so prevalent at this time of year.

A & W MEDICAL PRODUCT

WARD, BLENKINSOP & CO., LTD.

6, HENRIETTA PLACE, LONDON, W.1.

Makers of Ekammon for Safer Salicylate Therapy

Conclusion

When faced with a patient with persistent and intractable pain, for whom the continued administration of analgesic drugs is for any reason undesirable, the practitioner may do well to consider surgical treatment. This may comprise the severance of nerves or nerve roots or the pain pathways in the central nervous system, or their interruption or destruction by the injection of chemical substances such as procaine, alcohol, and phenol, or by electro-coagulation. If the patient's suffering is likely to be prolonged and the pain intense, and if the cause cannot be eradicated at its source, and addiction to morphine or its derivatives is an undesirable alternative, a good case may be made for employing surgical methods.

I am much indebted to my colleague Mr. Cecil Lewis, F.R.C.S., for the drawings.

Next Refresher Course Article.—"Glandular Fever," by Sir Henry Tidy.

THE CONTROL OF NEW REMEDIES*

BY

Sir WELDON DALRYMPLE-CHAMPNEYS, Bt.
D.M., F.R.C.P.
Deputy Chief Medical Officer, Ministry of Health

I have chosen "The Control of New Remedies" as the subject of my address because of an uneasy feeling that when new and powerful remedies are evolved the restrictions upon their use in the early stages may often seem unreasonable and even irritating to practitioners eager to give their patients the best treatment possible, and this in spite of the explanatory notices we put in the medical press.

Now, new remedies are of many different kinds and need control for many different reasons, ranging from the really dangerous untried remedy which must be carefully evaluated before doctors are in a position to use it safely to the harmless nostrum which may waste the private resources of the patient or the public resources of the Exchequer or postpone efficient treatment of some fatal disease until it is too late.

I propose to discuss first the control of those remedies usually known as "biologicals," and such control may be divided into three categories: (1) control of importation; (2) control of manufacture for sale; (3) control of distribution.

1. Control of Importation

The Government Departments primarily concerned with this form of control are H.M. Customs and Excise and the Board of Trade, but they depend on the Ministry of Health for expert advice where medical remedies are concerned. This is especially so in the case of those remedies which may be considered "therapeutic substances" within the meaning of the Therapeutic Substances Act of 1925—that is, substances "the purity or potency of which cannot be adequately tested by chemical means." These are the substances usually known as "biologicals," many of which are covered by the generic names of vaccine, toxin, antitoxin, antigen, but which include other substances specifically named in the schedule to the Act, such as insulin, surgical ligatures and sutures, the arsphenobenzene compounds, penicillin, blood products, etc. I will not go into the details of this Act and the necessarily complicated regulations made under it, which came into force in 1927, and which I have administered since 1928, but I would merely ask you to note that, though it provides a most valuable safeguard against the importation of dangerous or useless preparations of such substances, there are many others which, at any rate at first, are not caught by this net, either because they are of a kind to which the Act does not apply or because they are not mentioned, either individually or generically, in the Schedule to the Act. In such cases we have to consider whether the substance should be added to the Schedule if suitable, and whether on medical grounds we can recommend its admission to this country. Such advice is often difficult to give. For example, the antibiotics are being developed in a continuous stream, mostly in the United States, and the issue of each new one is accompanied by glowing claims for its effectiveness in a number of different infections. But we have to determine, in the first place, whether it is worthy of serious attention, and whether it is of sufficient importance to merit all the labour involved in devising a schedule to the Therapeutic Substances Regulations, laying down what tests for potency, toxicity, pyrogenicity, etc., it must pass. Even when we decide we must take it seriously it may still be a long time before satisfactory tests of this kind can be devised to safeguard the patient. In this task, however, the Medical Research Council gives us invaluable aid, though it cannot, of course, be expected to carry out such expensive and laborious investigations in the case of every remedy for which value is claimed.

I would here draw attention to some relevant considerations. First, we are often faced with applications to import a quantity of some new remedy "for research purposes." Obviously our pharmaceutical manufacturers, some of whom maintain research establishments of very high class, should not be hampered in their investigation of new remedies from abroad (on which they may often improve), but it must be remembered that "research" may mean something very far short of scientific investigation, and that the free distribution of new remedies to doctors is a well-established method of "creating a market," the customers in which may not be as discriminating as we would wish. The foreign manufacturers, moreover, well know that the new remedy, on the development of which they have perhaps spent vast sums of money, may be superseded in a short time by a superior rival, so they have got to recoup themselves as quickly as possible.

Of course, dollar expenditure has to be taken into consideration in making decisions (in 1951 we spent over $187,000, or nearly £67,000, on cortisone, and over $582,000, or more than £208,000, on A.C.T.H. and this year we shall be spending more), but fortunately this is an aspect on which the medical side of the Ministry is not expected to tender advice. I must, however, say a word about "free gifts," as this is a question with important medical bearings, and I will take cortisone as best illustrating my points. The importation of free gifts of medical remedies is usually permitted, though H.M. Customs can forbid it if they choose. Many kind persons in the United States, both medical and lay, have sent free gifts of cortisone to doctors here for use in particular cases, or direct to the patients themselves, and you may reasonably ask, "Why not?" Well, there is one very important consideration in such cases, apart from the danger of administration to the patient without proper control—namely, the starting of a treatment which cannot be maintained. I have received many, and often pathetic, appeals for cortisone for the treatment of patients with rheumatoid arthritis who have been greatly benefited by the injection of "free gift cortisone," the supply of which has failed. Usually I have been forced to refuse the request, though I knew that the last state of the patient would be worse than the first, because our limited supplies of cortisone—all that the manufacturers have been able to let us have—must, in fairness to the general body of patients and in order to obtain reliable information about its best method of use, be distributed to the 56 centres now holding it, where there are experienced physicians and adequate laboratory facilities.

And what of applications to import cortisone against dollar payments? Well, there are two cogent objections to allowing such applications. The first is that this means "jumping the queue," and that it would be unfair in prin-

*An address delivered to the Nottingham Medico-Chirurgical Society and the Nottingham Branch of the British Medical Association on February 27.

ciple for patients to obtain a remedy merely because they could pay for it, in preference to others whose needs are as great or perhaps greater. The second objection arises from the fact that in the United States cortisone is obtainable only on prescription—that is, for the treatment of an individual patient in America—so that any cortisone bought by private individuals in this country is obviously "black market."

2. Control of Manufacture for Sale

Let me take as an illustration of this aspect of control the antibiotics. It is well known that, after the demonstration by Fleming of the antibiotic properties of a culture of *Penicillium notatum* in 1928, a long interval elapsed until Florey and Chain at Oxford published their paper on penicillin in 1940. A valuable weapon had been evolved in the fight against infection, and the tremendous significance of such a discovery in the midst of a world war was immediately apparent. But, unfortunately, the pharmaceutical industry of this country was already hard pressed, and materials such as steel, which were essential to large-scale production of penicillin, were earmarked for other essential purposes. In these circumstances we had to turn to our friends (not yet our allies) in the United States, who, with their characteristic energy, quick grasp of the essentials, and genius for large-scale production, proceeded to produce on a tremendous scale this remedy, which played no mean part in winning the war.

Of course, under wartime conditions it was easy to keep a grip on penicillin, and this was true of the immediate post-war period, when production was started in this country but Defence Regulations were still in force. But a time came when a more permanent basis of control was needed—namely, control of manufacture to safeguard the patient from a toxic product or one of low potency; and control of sale and administration by unqualified persons to prevent the development of resistant strains and the masking of infection without curing it. For the first purpose the Therapeutic Substances Act of 1925 was eminently suitable, as penicillin is a substance "the purity or potency of which," as the Act has it, "cannot be adequately tested by chemical means." In 1944 penicillin was therefore added to the Schedule to the Act, and the Seventh Schedule was added to the Therapeutic Substances Regulations, defining what was meant by "penicillin" and the criteria to which it had to conform.

For the second purpose—namely, control of its sale and administration—an entirely new instrument was forged in the form of the Penicillin Act of 1947, which made it an offence for any person other than a duly qualified medical practitioner, a registered dental practitioner, or a registered veterinary surgeon, or a person acting in accordance with the directions of any such practitioner or surgeon, to sell or otherwise supply any substance to which the Act applied, such substances being penicillin in the first instance and then such other antimicrobial organic substances produced by living organisms as might be subsequently prescribed by the Licensing Authorities in England, Scotland, or Northern Ireland. The only antibiotic so far added has been streptomycin, by the Streptomycin Regulations, 1948.

3. Control of Distribution

The control of distribution is of course least difficult in the case of remedies manufactured abroad, as import licences are required, but the method is also applicable under certain conditions to remedies manufactured in this country. The control of "aureomycin" is an example of the first class of case and that of streptomycin of the second class. With regard to streptomycin, a procedure was evolved which we try to apply, with necessary modifications, to other cases. The first stage is that in which little is known of the new substance and the Ministry of Health imports (or, in the case of home manufacture, obtains exclusively by means of a "gentleman's agreement") a limited quantity for use by the Medical Research Council in working out the drug's dangers and uses.

The second stage is when the Medical Research Council advises us at the Ministry that the new remedy has given sufficiently satisfactory results in this preliminary trial to justify wider distribution and more extended trial. We then arrange for the remedy to be made available to certain centres selected for the facilities they possess in the way of clinical staff and laboratories for testing. Sometimes in return for the material we are supplying to the hospitals we ask them to keep certain records, so that experience can be pooled and evaluated to the benefit of all. It was in this way that in the autumn of 1947, soon after a wider distribution of streptomycin had been effected, I formed the Streptomycin Conference of representatives from the various centres which advised on the form these extended trials should take, and, by collecting and analysing the results, obtained some idea of the way in which streptomycin should be used in the treatment of tuberculous meningitis, with or without miliary tuberculosis, and the results which might be expected. It should be noted that this second stage may include, and in most cases has included, arrangements for making the antibiotic concerned available to general practitioners for use in certain specified conditions outside hospital, the conditions specified being those in which the Medical Research Council advises us that the remedy has been shown to be of definite value.

In the third stage the remedy is made available on prescription. This stage should logically be reached when the profession as a whole can be assumed to be sufficiently aware of the potentialities and dangers of the new remedy to use it with discretion, confining it to those conditions in which it may be expected to benefit the patient, and taking such precautions as will safeguard the patient, so far as is possible, from any undesirable side-effects. In practice, however, it is not always possible to wait until this desirable situation has been attained, and in order to make the remedy available for the treatment of patients outside hospital we must accept the prospect of some misuse and waste, a risk with which we are familiar in respect of many remedies which have long been available to the profession.

There might, of course, be a fourth stage, in which the remedy was made available to the public without a doctor's prescription, but the sort of remedies about which I am talking are all too dangerous for self-medication.

It will be realized that the decision when to transfer from one stage to the next is not an easy one to make, and that the considerations governing such a decision vary widely with the remedies concerned. Let me try to illustrate this point. In the case of penicillin, the toxicity was so low (once the product had been satisfactorily purified) that the only *medical* considerations affecting the decision to make it available on prescription were those which, as I have mentioned, led to the establishment of the special control provided by the Penicillin Act—namely, the possible emergence of strains of micro-organisms resistant to the antibiotic and the masking of disease by inadequate dosage. Thus the transition from stage two to stage three was an easy one and would, I think, have been taken without much hesitation even in ordinary circumstances; but time has shown, nevertheless, the reality of both the risks contemplated, and especially that of the emergence of resistant strains of micro-organisms.

Now, in contrast to penicillin, we hesitated long before transferring streptomycin from stage two to stage three, for here we had an antibiotic of marked toxicity, the use of which was fairly often associated wtih vertigo, tinnitus, and permanent deafness, though there is even now some doubt about how much these effects can be attributed to the antibiotic and how much to the disease for which it is given. In any case here was an antibiotic which needed treating with far more respect than penicillin, and when eventually we decided that, in view of the greatly increased scale of manufacture in this country, the extended experience in using it, and the demonstrated usefulness of this antibiotic in various penicillin-resistant infections, we ought to make streptomycin available on prescription, I was not the only person concerned who had serious misgivings.

The Control of Proprietary Remedies

So far I have been concerned with existing controls of new remedies, but it may be helpful to say a word about the so-called "proprietary remedies"—often wrongly referred to as "patent medicines."

The control of proprietary remedies is one of the most difficult and controversial subjects with which I have had to deal at the Ministry of Health, involving as it does such questions as the inevitability and innocuousness of simple self-medication, the freedom of the doctor to prescribe what he thinks best for his patient, the legitimate profits of the manufacturers, who claim that their ordinary "lines" must pay for the research needed to produce their "ethical remedies," and the proper method of determining what remedies are really needed and for what conditions it is justifiable to advertise them. These are questions in which the profession and politicians of all parties are interested, and which have been under active consideration at the Ministry for a very long time.

Now, proprietary remedies can be divided into two main categories—those advertised to the public and those, known as "ethical remedies," which are advertised only direct to the medical profession. Enormous sums of money are spent every year on remedies of the first class by the public in self-medication, and also by the State through prescriptions under the N.H.S.; and on remedies of the second class mostly by the State. I think there is pretty general agreement that a substantial proportion of this expenditure is wasted because the remedies are useless, inappropriately used, or unnecessarily expensive. For this reason many people think that there should be legal control of such remedies (apart from such control as I have already described, which applies entirely to the "ethical" remedies), but when one gets down to considering the appropriate form of control to apply there is a wide difference of opinion.

But first of all let us look rather more closely at the present position. It has been estimated that in 1951 about 229 million prescriptions were dispensed under the N.H.S. at an average cost of 3s. 11½d. per prescription, and of these about 20% by number and 40% by cost were for proprietary preparations. Though valuable new drugs have been developed at great cost by some proprietary firms, other firms, tempted by the facilities for prescribing afforded by the N.H.S., have merely duplicated standard preparations under proprietary names or have formulated medicines of doubtful therapeutic value at high prices. Such duplicate and doubtful medicines appear to constitute a major cause of the increase in the proprietary drug bill and their prescription to be the result of skilful propaganda to the doctors and advertising to the public which, of course, results in pressure on the doctor by the patient. The only existing control of proprietary remedies is that contained in Sections 11, 12, 15, and 16 of the Pharmacy and Medicines Act, 1941. Section 11 requires that every medicine (except one dispensed extemporaneously) shall bear on it a qualitative and quantitative statement of its content. Section 12 restricts the sale of medicines to doctors, dentists, authorized sellers of poisons, and persons who, before the passing of the Act, had served a pharmaceutical apprenticeship and sold drugs in a shop, *but* it is a defence under this Section to prove that medicine sold otherwise than as laid down under this Section was sold under a proprietary designation and was not described by name in the *British Pharmacopoeia* or the *British Pharmaceutical Codex*. Under Section 15 the Pharmaceutical Society has a duty to enforce Section 11, and under Section 16 the Food and Drugs Authorities have power to do so.

Section 11 places no limit on the duplication of proprietary remedies and no check on their therapeutic value. Section 12 allows such remedies to have a widespread sale. They can be prescribed under the N.H.S., and the only factors limiting such prescription are any deterrent effect which the second Interim Report of the Joint Committee on Prescribing (the Cohen Committee) may have had, and any action taken under the N.H.S. Regulations controlling excessive prescribing.

The problem of controlling proprietary remedies is not, of course, a new one. In 1914 a Select Committee of the House of Commons recommended the establishment of a register of remedies, the regulation of "fancy names" for recognized drugs, and the prohibition by a special Court or Commission of the sale of any remedy "in the public interest or on grounds of non-compliance with the law." The report was shelved during the 1914–18 war. In 1920 a Government Bill was introduced, but there was insufficient time to carry it through. In 1931, and again in 1936, private Members' Bills were introduced but made little progress. The possibility of such legislation was reviewed in connexion with the repeal of stamp duties, but the Pharmacy and Medicines Act, 1941, which resulted, was a compromise measure and did not tackle controversial issues.

As I have already pointed out, the advent of the National Health Service has made the position far more serious by the impetus it has given to the unnecessary multiplication of medicines and the intolerable burden thereby placed on the country's finances, so that the finding of a solution is a matter of urgent importance. It is worth noting in this connexion that France has recently taken drastic action to curb the production of unnecessary or valueless proprietary medicines. Following the introduction of legislation, manufacturers have been obliged to register their products and pay a fee for such registration, with the result that the 20,000 marketed proprietary medicines were reduced overnight to 8,000. These 8,000 were then classified therapeutically, and no new preparations were considered for entry on the register unless an expert committee decided that they represented a significant advance on those already available. The brand name of a particular drug has been restricted to the original manufacturer, and the prices of new products have been controlled. A number of other European countries are likely to follow this lead in the near future, and the probable effect of such a change on the British drug trade is obvious.

Effects of New Remedies

In conclusion, just a word about the possible long-term effects of the new remedies which have been and are being evolved at such a phenomenal rate. The resulting situation seems to me another case of the machine running away with us. Heaven forbid that we as medical men should reject or refuse to examine with the greatest care any remedy which may be of benefit to our patients, but we are being forced by circumstances at the present time to use many new remedies because of the immediate benefit they confer, whilst we are still ignorant of their long-term effect, either singly or in combination. For instance, can the sudden and radical changing of the flora of the upper respiratory passages and the alimentary canal by antibiotics like chloramphenicol be regarded with complete equanimity? Again, should we not regard with some apprehension the rapidity with which more and more strains of micro-organisms are being evolved which are resistant to more and more antibiotics, till perhaps we shall eventually reach the stage at which the race between the development of new antibiotics and the acquisition of resistance by the pathogenic organisms is won by the latter? Then what about cortisone and A.C.T.H.? Can it be safely assumed that such powerful hormones, given continuously over a long period as in rheumatoid arthritis, will have no deleterious effect upon other tissues than those whose disturbances have given the indications for such treatment?

And lastly, speaking as an epidemiologist, I find the interference by these hormones with skin reactions, which are such valuable aids in the diagnosis of infection and the estimation of resistance, disturbing to say the least of it.

Certainly we all carry a very heavy responsibility at the present time, and, if the policy of the Ministry of Health seems at times over-cautious, perhaps the memory of what I have recorded here may make our actions appear more reasonable in your eyes.

SIR WILLIAM SAVAGE, 80

Sir William Savage, a leading figure in preventive medicine for many years past, reached his eightieth birthday on August 15, and we take this opportunity to wish him many more years of active life. He continues to pursue his researches into subjects that interest him with as much energy and enthusiasm as ever; only a few weeks ago we published a review of his latest book, *The Making of our Towns*.

The name of Savage will always be associated with food-poisoning, and particularly with salmonella infections. As early as 1908 he was reporting the isolation from animals

[Lafayette, London

of what at this time he called the Gaertner group of bacilli, and it was his early studies on the aetiology of food-poisoning outbreaks that led the Medical Research Council to sponsor investigations by himself and Bruce White into the serology of the salmonella group and their relationship to food-poisoning. Two M.R.C. "green reports" within a year (Nos. 91 and 92) firmly established the relationship between various salmonella types and food-poisoning, and showed that domestic animals and vermin were the main reservoirs of these organisms.

Sir William has always been a strong advocate of milk pasteurization and shown a keen interest in the hygiene of milk and food. Recently he acted as a very able and energetic chairman of the working party on hygiene in catering establishments. Among his better-known books are *Milk and the Public Health* (1912), *Bacteriological Examination of Food and Water* (1914), *Canned Foods in Relation to Health* (Milroy Lectures, 1923), and *The Prevention of Human Tuberculosis of Bovine Origin* (1929).

Sir William Savage has had a career in the public health service which all medical officers of health must envy. Not only did his original contributions place him in the forefront of scientific investigators, but the practical results of his work were of direct and immediate benefit to the public whom he served. After qualifying at University College Hospital in 1896 he held a number of academic posts as a pathologist and bacteriologist. In 1909 he became the first county medical officer of health of Somerset, a post he retained until his retirement in 1937. In his early days by necessity, and later by strong conviction through years of experience, he was a great upholder of the vital importance of adequate environmental standards in the promotion of public health. In Somerset, being the first county medical officer, he was unhampered by anything which had gone before, and so he was able to mould his department (and this suited his character admirably) in his own way and according to his own views, and all this he did with great competence and diligence. Perhaps his clarity of mind, not the least dimmed by the passing years, has been his greatest asset in all his work. He was always a strong medical officer—suffering both professional and lay fools badly—and no opposition or criticism has ever turned him from any purpose in which he believed.

In the 15 years of his retirement (if such a word can ever be applied to him) Sir William has enjoyed his Somerset garden, his walks, and his tennis, and even at the age of 80 he plays men's doubles, as a rule giving the other players a start of some 30 or 40 years and easily keeping up with them. In work and in play for nearly half a century in Somerset Savage has never spared himself, and he has enjoyed both with a zest undiminished by the weight of years.

Reports of Societies

SECOND INTERNATIONAL CONGRESS OF BIOCHEMISTRY

During the first International Congress of Biochemistry, initiated by the Biochemical Society and held at Cambridge in August, 1949, the invitation of the Société de Chimie Biologique to hold the second Congress in Paris in 1952 was accepted. The French society must indeed have been gratified by the enrolment of more than 2,000 members of more than 40 different nationalities for this meeting in Paris from July 21 to 28.

It opened with an impressive ceremony in the Great Amphitheatre of the Sorbonne. Speeches of welcome by the Président d'Honneur, Gabriel Bertrand (member of the Academies of Science, Medicine, and Agriculture), by Professor Claude Fromageot (president of the executive committee), and by Doyen René Fabre (President of the Congress and general secretary of the Société de Chimie Biologique) were interspersed with music from the band of the Garde Républicaine. The reading of papers began at 2 p.m. on July 21, and continued in the many lecture theatres of the Sorbonne until 5 p.m. on July 26. In this time the enormous total of more than 800 papers were read and discussed.

Plan of the Congress

The work of the Congress was divided into seven symposia and 31 sections. In each symposium there were about 10 reports—formal lectures delivered in the mornings—and in both the symposia and the sections there were large numbers of original communications limited to 10 minutes each, with five minutes for discussion. In addition, there were four general afternoon lectures delivered during the week: Professor J. N. Davidson (Glasgow) spoke on "Nucleoproteins and tissue growth," Academician A. I. Oparin (Bach Institute of Biochemistry, U.S.S.R.) on "The changes in enzymic action in plant cells under the influence of external factors," Professor S. Ochoa (New York) on "Carbon dioxide fixation in plants and animals," and Professor K. Linderström-Lang (Copenhagen) on "Proteins and enzymes."

The subjects of the 31 sections ranged from mineral elements, lipids, amino-acids, proteins, and pigments through numerous specific groups of enzymes to fermentations, plant chemistry, photosynthesis, nutrition, chemotherapy, and even apparatus and techniques. It would be

difficult to think of a biochemical research which could not have found a congenial place in one of the reports or symposia. Only three short papers, in fact, found their way to the thirty-second section—"Miscellaneous." It is an almost impossible task to choose at random from the many papers delivered in the sections a few which might be classed as representative. The scope of the Congress and the trends of modern biochemical research are amply illustrated by brief reference to the symposia.

Blood and Proteins

Symposium 1. Biochemistry of Haematopoiesis.—The subjects ranged from "The structure of haemoglobin" (M. F. Perutz, Cambridge) to "The cytochemistry of bone marrow" (M. Errera, Brussels). Folic acid and vitamin B_{12} and their related compounds, of course, figured largely, the emphasis being on non-clinical aspects such as chemistry, assay, and biochemical functions. There were descriptions of haem and porphyrin synthesis in blood *in vitro*, studied with and without the aid of isotopically labelled compounds, by French, American, and English workers. Among these papers were the first reports of *in vitro* haem synthesis by haemolysates of nucleated erythrocytes, and it is apparent that the way should now be open to the discovery of part of the enzymic control of haemoglobin biosynthesis.

Symposium 2. Biogenesis of Proteins.—The reports in this field included "The biosynthesis of peptide bonds" (J. S. Fruton, New Haven), "Adaptive enzymes" (J. Monod, Paris), "The dynamic state of tissue proteins" (D. Rittenberg, New York), "The biosynthesis of milk proteins" (T. S. Work, P. N. Campbell, and B. A. Askonas, Mill Hill, London), and "The problem of the precursor in the induced synthesis of enzymes" (S. Spiegelman, St. Louis). In the communications the emphasis was again on the biosynthetic aspects. For example, M. Brenner and A. Vetterli (Basle) spoke on "The enzymatic synthesis of dipeptides from free amino-acids," and H. Borsook and collaborators (California Institute of Technology) on "The *in vitro* incorporation of labelled amino-acids into reticulocyte proteins."

Intracellular Chemistry

Symposium 3. The Tricarboxylic Acid Cycle.—Though of less direct interest to medical readers, this subject occupies a very important place on the broad advancing front of biochemistry, since it is the basis of respiration by the tissues, and of their production of carbon dioxide, as well as involving the final breakdown of carbohydrate. Much of the work is done with preparations of intracellular particles, the mitochondria, and it is from these studies that the complexities of cellular organization are beginning to emerge. One of the most important recent discoveries has been the recognition and characterization of coenzyme A, an essential pantothenic-acid-containing activator of the natural enzyme which catalyses acetylations (for instance, the synthesis of acetylcholine from choline), and also the entry of two-carbon compounds into the metabolic cycle of the tissues by combination with a citric acid cycle derivative. Thus among the reports were "The enzymatic synthesis of citric acid" (S. Ochoa, New York), "The role of coenzyme A in two-carbon fragment condensation" (F. Lipmann, Boston), and "The entry of metabolites into the tricarboxylic acid cycle" (C. Martius, Tübingen).

Symposium 4. Protein-hormones and Hormones Derived from Proteins.—The large number of papers dealing with A.C.T.H. and with thyroid biochemistry reflected the intense activity in these fields over the last few years. Reports were given on A.C.T.H. by C. H. Li (California), on the thyroid by R. Michel (Paris), and on the isolation and structure of oxytocin and vasopressin by V. du Vigneaud (New York).

New Thyroid Substance

An interesting development in thyroid biochemistry is the discovery of 3:5:3′ triiodothyronine—that is, thyroxine without its fourth iodine atom at position 5′. J. Gross and R. Pitt-Rivers (Mill Hill, London) have isolated this compound from thyroid tissue and have found that it is several times more effective than thyroxine. It is identical with a previously unrecognized substance reported in plasma and in the butanol extract of unhydrolysed thyroid. The same compound has been studied by S. Lissitzky, R. Michel, and J. Roche (Paris), who found that it is a constituent of thyroglobulin, together with thyroxine and with traces of 3:5-diiodothyronine. With the aid of radioactive iodine these workers have followed the formation of thyroxine and triiodothyronine in the thyroid gland and the plasma of rats, and have also made some studies of the metabolism of the new amino-acid. Another protein hormone, insulin, received a good deal of attention, and one of the interesting papers was that of K. H. Möller, M. Jersild, K. Petersen, and J. Schlichtkrull (Copenhagen), who described a suspension of crystalline insulin, a single injection of which suffices to maintain the blood sugar level in man constant within a few per cent. for 24 hours.

Other Matters

Symposium 5. Microbial Metabolism.—The accent throughout was on growth factors, biosynthesis, and catabolism in micro-organisms. In *Symposium 6 (The Mode of Action of Antibiotics)* reports were given on the mode of action of P.A.S. and derivatives (S. Americano-Freire, Brazil), of penicillin (H. Machebœuf and F. Gros, Paris), and of streptomycin (W. W. Umbreit, New York); on the biochemistry of acridines (L. Massart, Ghent), on the effect of antibiotics on amino-acid assimilation in bacteria (E. F. Gale, Cambridge), and on the cytological study of the mode of action of antibiotics (J. Dufresnoy, San Francisco). In *Symposium 7 (The Biochemistry of Steroids)* the main emphasis was of course on the adrenocortical steroids. A good deal of progress in studies of the biosynthesis of steroids was reviewed by C. Pincus (Shrewsbury, Mass.).

All members of the Congress were given a book of abstracts of all the original communications (2e *Congrès Internationale de Biochimie*, Résumé des Communications, Paris, 1952), and the full text of the reports of the seven symposia were available for purchase, and are available through booksellers in England at £4 8s. the set. The next Congress will be at Brussels in 1955.

ORDER OF ST. JOHN OF JERUSALEM

The *London Gazette* has announced the following promotions in, and appointments to, the Venerable Order of the Hospital of St. John of Jerusalem:

As Knight: Dr. F. W. M. Palmer. *As Commanders (Brothers):* Colonels J. P. J. Jenkins, O.B.E., T.D., M.R.C.S., and R. M. Morris, O.B.E., M.D., Air Marshal J. MacC. Kilpatrick, C.B., O.B.E., M.B., Air Vice-Marshal W. E. Barnes, C.B.E., M.R.C.S., L.R.C.P., Air Commodore F. E. Lipscomb, M.R.C.S., L.R.C.P., and Drs. D. M. MacManus, G. Rocyn-Jones, J. Mackenzie, and G. A. Macdonald. *As Commanders (Sisters):* Drs. Gladys A. Danby, M.B.E., Cecily Porter, and May Rutledge. *As Officers (Brothers):* Surgeon Captains J. G. Holmes, O.B.E., M.D., and R. L. G. Proctor, M.D., F.R.C.P.I., Surgeon Lieutenant-Commander the Hon. A. G. Gathorne-Hardy, M.B., R.N., Major-General E. H. Hall, O.B.E., M.B., Colonel T. I. Dun, D.S.O., *M.C.*, M.B., Majors H. C. Stewart, M.D., M.R.C.P., and A. W. E. Soysa, O.B.E., M.B., M.R.C.P., Captain P. M. Gettleson, M.D., Group Captain J. Kemp, M.B., Mr. M. A. Paul, M.S., F.R.C.S., and Drs. G. Busuttil, K. D. Bean, E. J. G. Wallace, K. M. Macdonald, L. M. Maybury, H. R. Wynne, T. E. Wood, A. B. Davies, H. Rosenberg, N. MacLeod, E. P. Coyne, S. G. Budd, R. L. Cheverton, D. R. McPherson, H. M. Shelley, D. H. Kinmot, E. H. Eastcott, A. R. McPherson, S. C. H. Lane, O. H. Bostock, Pah-Chien Kwan, T. Hambly, J. V. Shemilt, A. M. Pollock, J. D. Sinclair, O.B.E., A. C. Brown, A. B. Badger, T. Ruddock-West, and K. D. Young. *As Associate Officer (Brother):* Dr. S. B. Malik, O.B.E. *As Serving Brothers:* Surgeon Commander J. M. Reese, M.R.C.S., L.R.C.P., Major R. S. Adam, M.B., and Drs. G. M. S. Smith, I. Mackenzie, J. Fleming, G. McD. Mitchell, M. Theodoulou, H. Symeonides, G. M. Pietroni, P. Hajieftychios, A. Bury, T. H. Kirk, R. G. Russell, T.D., S. M. Davidson, A. G. Walker, H. MacCallum, and S. G. Meanley. *As Associate Serving Brother:* Dr. L. Saville. *As Serving Sisters:* Drs. Catherine J. Clark, Ethel W. Kirk, and Clara Stewart.

HER MAJESTY'S HOUSEHOLD

THE MEDICAL APPOINTMENTS

A *Supplement* to the *London Gazette* of August 5 announces the following medical and dental appointments to Her Majesty's Household:

Physicians:
Sir Horace Evans, K.C.V.O., M.D., F.R.C.P.
Sir John Weir, G.C.V.O., M.B., Ch.B.
Ronald Bodley Scott, D.M., F.R.C.P.

Physician-Paediatrician:
Wilfrid Percy Henry Sheldon, M.D., F.R.C.P.

Extra Physicians:
Lord Horder, G.C.V.O., M.D., F.R.C.P.
Sir Henry Letheby Tidy, K.B.E., M.D., F.R.C.P.
Sir Daniel Thomas Davies, K.C.V.O., M.D., F.R.C.P.

Sergeant-Surgeon:
Sir Arthur Porritt, K.C.M.G., C.B.E., M.B., M.Ch., F.R.C.S.

Surgeons:
Sir James Paterson Ross, K.C.V.O., M.S., F.R.C.S.
Ralph Marnham, M.Chir., F.R.C.S.

Surgeon-Gynaecologist:
Sir William Gilliatt, K.C.V.O., M.D., M.S., F.R.C.P., F.R.C.S., F.R.C.O.G.

Extra Surgeons:
Sir Thomas Peel Dunhill, G.C.V.O., C.M.G., M.D., Hon.F.R.C.S., F.R.A.C.S.
Sir James Walton, K.C.V.O., M.B., M.S., F.R.C.S.
Sir Lancelot Edward Barrington-Ward, K.C.V.O., Ch.M., F.R.C.S.

Extra Manipulative Surgeon:
Sir Morton Smart, G.C.V.O., D.S.O., M.D.

Extra Surgeon-Apothecary:
Sir Frederick Stanley Hewett, K.C.B., K.C.V.O., K.B.E., M.D.

Surgeon-Oculist:
Sir Stewart Duke-Elder, K.C.V.O., M.D., D.Sc., Ph.D., LL.D., F.R.C.S., F.A.C.S.

Extra Orthopaedic Surgeon:
Sir Reginald Watson-Jones, M.Ch.Orth., F.R.C.S., F.R.A.C.S., F.A.C.S.

Aurist:
John Douglas McLaggan, C.V.O., M.B., Ch.B., F.R.C.S.

Surgeon Dentist:
Alan Cumbrae Rose McLeod, F.D.S. R.C.S.(Eng.), D.D.S.

Extra Physician to the Household:
Sir Arnold Walmsley Stott, K.B.E., B.Chir., F.R.C.P.

Surgeon-Oculist to the Household:
Allen John Bridson Goldsmith, M.B., B.S., F.R.C.S.

Extra Surgeon-Oculist to the Household:
Frank Anderson Juler, C.V.O., M.B., B.Ch., F.R.C.S.

Apothecary to the Household:
John Nigel Loring, M.R.C.S., L.R.C.P.

Surgeon-Apothecary to the Household at Windsor:
Richard William Legerton May, M.B., B.Chir.

Extra Surgeon-Apothecary to the Household at Windsor:
Edmund Claud Malden, C.V.O., M.B., B.Chir.

Surgeon-Apothecary to the Household at Sandringham:
James Lawrence Bunting Ansell, M.R.C.S., L.R.C.P.

MEDICAL HOUSEHOLD IN SCOTLAND

Physicians:
Alexander Greig Anderson, C.V.O., M.D., LL.D., F.R.C.P.
Sir John William McNee, D.S.O., M.D., D.Sc., F.R.C.P.
Professor Leybourne Stanley Patrick Davidson, M.D., F.R.C.P.

Surgeons:
Sir James Rognvald Learmonth, K.C.V.O., C.B.E., LL.D., Ch.M., F.R.C.S.Ed., Hon.F.R.C.S., Hon.F.A.C.S.
George Gordon Bruce, M.B., Ch.B., F.R.C.S.

Surgeon-Oculist:
John Marshall, *M.C.*, T.D., M.B., Ch.B., F.R.F.P.S.

Surgeon-Dentist:
Robert Charles Scott Dow, L.R.C.P.&S.Ed., H.D.D., F.D.S.

Surgeon-Apothecary to the Household at Balmoral:
George Proctor Middleton, C.V.O., M.B., Ch.B.

Surgeon-Apothecary to the Household at the Palace of Holyroodhouse:
George Brewster, M.D., D.P.H.

Coroner of the Household:
Lieutenant-Colonel William Hilgrove Leslie McCarthy, D.S.O., *M.C.*, M.D., M.R.C.P., D.P.H.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Confused Nomenclature

SIR,—The letter of Dr. H. Gordon Oliver (August 2, p. 283) gives another illustration to a point I made recently in relation to the term "megacolon": the confusion caused in our profession by calling different things by the same name. Among the babies sent up to my clinics with the diagnosis of "talipes equino-varus," it is seldom that there is not one or more in the course of a week which I dismiss as simply "inversion spasm," needing no treatment. Yet, as the feet (though normal) are persistently held in equino-varus, the condition is congenital, and, as textbooks speak of "paralytic talipes" and "spastic talipes," they can certainly be described as "congenital talipes equino-varus." What they are not are club-feet, and it would be unfortunate if Dr. Oliver's letter should lead anyone to suppose that a true club-foot can be easily and quickly corrected. An experience of many thousands of such cases, beginning with the watching of such masters as Sir Robert Jones and Sir Thomas Fairbank, has taught me only too thoroughly that they cannot.

The optimism of those who claim to cure "talipes" by a few simple plasters or by massage is due to their experience being confined to inversion spasm; just as the optimism of those who "bring down testicles from the inguinal canal" by hormones is due to the results gained with normal retractile testicles. Of the latter I see about three or four a week throughout the year, and, like the inversion spasm of the feet, they give perfect results with or without treatment.

Another example of this type of confusion is supplied by the correspondence on pilonidal sinus. This is now running at complete cross-purposes, owing to grouping together (1) a rare and dangerous congenital deformity, which I personally class as a variety of spina bifida, and (2) an acquired condition, of various origins, resulting in hairs either getting into, or growing out of, a sinus. No one so far has brought in the result of Bucknall's operation on a hypospadias as an example of an acquired "pilonidal sinus," or the not uncommon dermoid of the nose as a congenital one.—I am, etc.

London, W.1. DENIS BROWNE.

Peptic Ulcer and the Neurotic

SIR,—I read with interest and profit the article on peptic ulcer by Professor C. F. W. Illingworth (July 26, p. 206). I was, however, rather disturbed by the following statement which occurred in the paragraph under the heading of psychotherapy. He states: "In this connexion it should be recognized that, while many neurotics *invent* [italics mine] digestive disturbances, the ranks of genuine ulcer cases contain no higher proportion of neurotics than does the population at large. Most ulcer patients, indeed, are the reverse of neurotic. They may be anxious and worried, but they never *invent* symptoms, generally make light of their suffering, and rarely give up work unless the pain is intolerable."

I agree entirely with what he says about the temperament of the ulcer patient, but I cannot agree when he says that "many neurotics invent digestive disturbances." Such a statement implies that many neurotics deliberately and consciously lie in saying that they have pain or discomfort when in fact they have not. The effect of this is practically to equate many neurotics with malingerers. This, in my experience—and I believe I may say in that of most psychiatrists—is quite untrue. It is extremely rare for a neurotic to be a malingerer. They are in fact very different types of personality.

His use of the word "neurotic" would also appear to imply an extremely narrow concept of the meaning of the term, and practically to equate it with self-indulgent hypochondriacs. Since these mistaken ideas are all too prevalent among both doctors and members of the general public, and frequently lead to a complete misunderstanding of certain types of patient and to a degree of mishandling which on occasions amounts to little short of mental cruelty, it is most unfortunate that Professor Illingworth, whose opinions naturally carry great weight, should appear to support these misconceptions.—I am, etc.,

London, W.9. DORIS M. ODLUM.

SIR,—The article by Professor C. F. W. Illingworth on peptic ulcer (July 26, p. 206) includes the statement that "most psychiatrists now agree that formal psychotherapy has no place in the treatment of an established ulcer." Statements of this kind do not lend themselves to proof or disproof, but it would perhaps be fair to say that as an expression of opinion this appears to ignore completely the contributions of Drs. Stewart Wolf and H. G. Wolff, and Dr. Frank K. Abbot, from Cornell University Medical College and the New York Hospital. The effective combination of psychotherapy with medical or post-operative surgical treatment is also practised in Guy's Hospital, and in other hospitals in this country.

In the same paragraph there occurs also the all-too-common fallacy of confusing neurotic illness with malingering. This leads to a tendency to brand patients with a neurotic basis to their symptoms as essentially undeserving cases, and results in a prejudiced approach to the entire problem. It is only because of the authoritative nature of the series in which this article appears, and the undeniable eminence of its author, that I have felt bound to draw attention to these controversial and, in my opinion, subjectively biased observations.—I am, etc.,

London, S.E.1. D. STAFFORD-CLARK.

Danger from Cuffed Endotracheal Tubes

SIR,—Dr. G. A. Eason's letter (August 2, p. 283) impels me to draw attention to another danger, which seems not to be generally known, of this type of tube.

It may easily happen, when the tube is inflated in the trachea, that the lower end of the tube is drawn up into the cuff, so that the cuff obstructs the lower end of the tube and asphyxia results. The observations that I now make are based on the evidence at a recent inquest, and the very experienced anaesthetist who then gave evidence had not been aware of this particular risk or experienced it previously. There was also evidence that recently some manufacturers had been shortening that part of the tube beyond the cuff, and that this shortening would render more likely the overriding of the lower opening by the cuff in this way.

I write because it seems desirable that some publicity should be given to this particular risk and because, according to the evidence given at the inquest, if the position is appreciated and immediately recognized the obstruction can be immediately relieved by pushing the tube farther into the trachea—a manœuvre which will restore the tube to its proper position.—I am, etc.,

Leatherhead. C. F. J. BARON.

Social Trends and Home Confinements

SIR,—I was prompted to write to you in the first instance (June 7, p. 1246) because of Dr. W. N. Leak's contention (May 24, p. 1135) that domiciliary midwifery is safer than institutional. In Aberdeen in 1946–7 (the last years in which many primiparae were confined at home) the stillbirth rate was 30% higher among domiciliary than among booked hospital primiparae, and more domiciliary deaths were due to asphyxia and birth trauma—complications which might have been avoided by different management of labour. It has been suggested that these findings are not typical of other areas, but Dr. Ivor Cookson's figures (July 19, p. 159) show that during 1949–51 in a West Country area the stillbirth rate was 23% higher among domiciliary than among booked hospital primiparae.

Dr. Cookson points out that to save the two or three stillbirths involved would have meant the admission of 365 patients to hospital, at a cost of four extra hospital beds and cots. Although he does not actually say so, it looks as though he considers that the return for such a service would be rather small. As I indicated in my original letter, the planning of a maternity service so that national resources can be used to the best advantage for all is much too complicated a subject to be dealt with in a letter; but the available evidence shows that hospital confinement is safer.

The latter part of Dr. Cookson's letter illustrates the difficulty of making valid statistical comparisons between the results of domiciliary and hospital confinements, owing to selection factors. He shows that extreme prematurity was much greater in the domiciliary group and that this was an important factor in deciding the stillbirth rate, but does not say whether hospital figures were weighted by cases sent to hospital because they were likely to have a difficult labour. Another question which may cause confusion is what is meant by hospital confinement. In some instances it means that the family doctor, responsible for his patient throughout, delivers her in a small maternity hospital rather than at home. It would seem reasonable to assume that he could work more safely in a hospital specially built, equipped, and staffed for the purpose. In other cases it means that patients are under the care of specialists from the beginning of pregnancy, and that during labour a uniformly high standard of care is readily available, including the services of expert anaesthetists and, nowadays, of a resident paediatrician. It would be strange indeed if all this specialization and concentration on detail did not achieve something. The fact is, of course, that in all areas the "bad risk cases" are concentrated in such a hospital. Why, then, should we search around for statistics to show that hospital confinement suddenly becomes more dangerous than home confinement for the more "normal" case?

If Dr. Cookson has read any of my publications on stillbirth, he will know that I believe that the standard of health, nutrition, and living conditions of mothers have a relatively greater influence on the stillbirth rate than the standard of obstetrical technique during labour. Nevertheless, experienced obstetricians working under ideal conditions in hospital can save both maternal and infant lives which would otherwise be lost. There seems to be no room for doubt that in a well-equipped and well-staffed maternity hospital the "hazards of birth" are less than in domiciliary practice; in other words, that hospital confinement is safer.—I am, etc.,

Aberdeen. DUGALD BAIRD.

Symptomatic Purpura during Isoniazid Therapy

SIR,—A toxic reaction to isoniazid is reported here in view of the widespread interest in this new antituberculosis drug.

A man aged 34 developed a tuberculous infection in the extrapleural space following thoracoplasty, and was treated first with streptomycin and P.A.S. Isoniazid was added two weeks later in a dose of 50 mg. twice daily for the first week and thereafter of 50 mg. four times daily. After 28 days on this combined therapy he developed suddenly a severe and widespread purpuric rash involving the limbs and trunk. At the same time he complained of pain in his joints. There was no history of previous skin trouble or of allergy of any kind. The patient was not taking any other drug known to produce purpura.

For six days he ran a remittent pyrexia which reached a maximum of 101.2° F. (38.4° C.). The rash was typically purpuric in the initial stages, tending to coalesce after 48 hours. Both knee and elbow joints were swollen, reddened, and stiff, with increase in local heat. Within two days both wrists and the first metacarpo-phalangeal joints of each hand had become similarly affected. The fundi and mucous membranes showed no evidence of haemorrhage. The capillary resistance test was negative. There were no abnormal signs to be found in the other systems apart from the renal tract. The urine was heavily blood-stained (200–300 red

cells per high-power field) and there was a heavy cloud of albumin with many hyaline and granular casts. The specific gravity was 1035. When admitted to hospital four months before, the urine had shown a faint trace of albumin and 40 red cells per field. At that time these findings were attributed to the large amount of streptomycin and P.A.S. he had received previously, as a thorough renal tract investigation revealed no other cause. The bleeding time (3 minutes 25 seconds), clotting time (6 minutes), platelets (400,000 per c.mm.), prothrombin time (17 seconds, control 16.2 seconds), leucocytes 12,000 (polymorphs 66%, lymphocytes 28%, eosinophils 1%, mononuclears 5%), and blood urea (33 mg.%) were all within expected limits. The stools remained negative for occult blood.

Isoniazid was now discontinued, with improvement in the skin and joint lesions. On being given isoniazid, 50 mg., on three successive days, after an interval of 10 days during which he remained on streptomycin and P.A.S., he had a recrudescence of the previous symptoms and signs.

All chemotherapy was then omitted. The joints returned to normal, but the rash varied in intensity from day to day before eventually clearing except for a small area along the left forearm. Three weeks later the isoniazid was again exhibited. Two 50-mg. tablets were given at a 12-hourly interval. This was followed at once by an acute flare-up of the symptoms, which subsided when the drug was stopped except for the rash, which has continued to wax and wane. There was no appreciable change in the number of platelets during the second and third episodes.

Two courses of streptomycin and an 18-months course of P.A.S. had been given in the past without any untoward effect. It would therefore appear that this case of symptomatic purpura was directly due to a toxic effect of isoniazid not previously reported in this country.

I wish to thank Mr. Vernon C. Thompson for permission to publish this case.—I am, etc.,

London Chest Hospital, Arlesey, Beds. D. M. COLLINS.

Isolation and Quarantine

SIR,—Dr. G. W. Ronaldson's letter (July 26, p. 227) requires an answer. I am content to receive all that Dr. Ronaldson has said about streptococcal and meningococcal infections, but I think we may be speaking of different conditions—he about discharge from hospital, I about letting discharged patients mix freely with all and sundry. "Absence of return cases" is, I admit, a good criterion of effectiveness of isolation, but those exposed at home are few, especially to-day. However, I am generally in agreement that I was over-cautious in Table III; this was really meant to be so, but I stated there were no hard-and-fast rules.

His comments on chicken-pox and scabbing include reference to F. H. Thomson (*Lancet*, 1916, **1**, 341), and after reading this carefully I think Dr. Ronaldson has drawn unjustifiable conclusions. Thomson never said, "Each spot is infectious for three days only." What he did say is, "Although it is safe to treat chicken-pox at certain stages of the disease in this special ward with all its precautions against direct and indirect contact infection, it does not follow that it would be safe to treat it in a similar, or even scabbing stage, in an ordinary ward where no such precautions are taken." The stage he referred to was the third day of the poxes, and some patients at this stage infected those exposed, although they were kept in bed and often had in each bed on both sides a child protected by a previous attack. We still do not know how long a child is infectious with chicken-pox, and I still think that with good treatment in healthy individuals the scabs can be cured in 12–16 days from the onset. If Dr. Ronaldson would suggest the time should be cut to six days whether scabs are present or not and that the small risk of spread be taken, I would agree, because I feel the sooner this trivial disease is over the better.

Lastly, let me say that Table II was condensed from another table, and that during this process some headings were most unfortunately altered. The full table is given at the foot of this page.

This shows that no quarantine was imposed, but all the 203 were under surveillance, and I hope Dr. Ronaldson will agree that this shows a good record for surveillance.—I am, etc.,

Rugby. R. E. SMITH.

Death from Penicillin

SIR,—In the *Journal* of July 12 (p. 70) there is a report by Dr. W. O. Thomson of a case of sudden death following an injection of crystalline penicillin G. I have had a similar experience with a child aged 3½ years who died some three and a half hours after an intramuscular injection of procaine penicillin. He had had a similar injection the day before. Approximately one hour following the second injection he lost consciousness and became dyspnoeic; he died some two and a half hours later. Post-mortem examination showed a very few petechial haemorrhages on the surface of the lungs and brain and gross pulmonary emphysema. There was no history of previous asthma or other allergy, nor had there been any symptoms or signs of any pulmonary trouble previously.

I also had a patient who during the giving of an intramuscular injection of procaine penicillin became unconscious and had a convulsion; he soon recovered. The nurse who was giving the injection was quite certain that the needle was not in a vein, as she had made sure of this by attempting withdrawal of the piston of the syringe. In the *Journal* of February 10, 1951 (p. 299), Dr. T. V. Humphreys describes a case in which a few minutes after an injection of procaine penicillin the patient became apprehensive and dyspnoeic and had a swollen tongue, urticaria, and convulsions; this patient responded to "anthisan" and adrenaline administration. Dr. Thomson gave his patient adrenaline and nikethamide without effect. A. Yuval (*Lancet*, 1952, **1**, 163) reports the case of a patient who within a few minutes of an intramuscular injection of procaine penicillin developed unconsciousness and stertorous breathing; the patient recovered. R. C. L. Batchelor and others (*Lancet*, 1951, **2**, 195) mention a feeling of impending death in a patient following an injection of procaine penicillin. I also have had such a case.

In the *Journal* of June 2, 1951 (p. 1269) there is a report on a child who died some days after the application of penicillin ointment to burns. In this case there were oedema and collapse of the lungs and a pericardial effusion causing cardiac embarrassment. Some other fatalities from penicillin treatment have been reported in Swiss, French, and American publications.

We should be aware that these allergic or anaphylactic fatal reactions can follow treatment with procaine penicillin, or crystalline penicillin without procaine, and it would seem worth bearing in mind that giving anthisan and adrenaline, preferably intravenously, may in these very rare cases avert a fatality.—I am, etc.,

Warwick. J. A. HARPMAN.

Results of Surveillance of 203 Boys Exposed to Infection (1933–47)

Disease to which Boy was Exposed	Measles	Mumps	Rubella	Pertussis	Chicken-pox	Scarlet Fever	Total
Total No. of boys exposed	42	52	28	22	32	27	203
Previous attack*	32	14	11	15	23	14	109
No previous attack	10	38	17	7	9	13	94
Quarantine usually advised (days)	16	30	21	21	21	10	
Days lost if all quarantined	672	1,560	588	462	672	270	4,224
Days lost if only those with no previous clinical attack* quarantined	160	1,140	357	147	189	130	2,123
No. of boys attacked	0	2	0	1	0	0	3

* Or Dick-negative.

Lithopaedion in African Women

SIR,—Dr. F. Schwarz (July 19, p. 131) in reporting this case says he has not been able to find a single report of a lithopaedion in an African. It may therefore be worth noting that I found a lithopaedion at laparotomy in a Kenya African (Luo tribe) about three years ago. A note of the case was published in the *East African Medical Journal* (1951, 28, 90) with references to other cases, at least one of which was also in an African woman.—I am, etc.,

Maseno, Kenya. R. B. LEECH.

Is Metallic Mercury Poisonous?

SIR,—I should like to comment on the article by Drs. Gilbert Forbes and James White (April 26, p. 899) and the letter of Mr. R. S. Handley (May 24, p. 1131) on the subject of metallic mercury poisoning. The frequency with which silver amalgam fillings are placed into excavated teeth should be sufficient to convince those who are interested that metallic mercury is not excessively poisonous. In the course of the insertion of the average silver amalgam dental filling a considerable portion of mercury which is uncombined with the alloy filling material is expressed prior to insertion into the cavity. Therefore quite an amount of relatively uncombined mercury remains in contact with the oral mucous membrane even following insertion of fillings. Also, the patient inadvertently, but very frequently, swallows small bits of silver amalgam which have been left in the mouth following carving. These bits of silver, which are swallowed, contain considerable amounts of uncombined mercury owing to the fact that they were the last carved-off portions of amalgam, in which the uncombined mercury content is extremely high. Although there have been some instances of sensitivity to silver fillings reported in the literature, these have been extremely rare considering the total number of dental fillings placed.—I am, etc.,

School of Dental and Oral Surgery, Columbia University, New York. AUSTIN H. KUTSCHER.

Chronic Lead Poisoning

SIR,—I have read with interest the contribution of Dr. Jane M. Fullerton (July 19, p. 117), in which she sets forth the haematological findings in a group of lead workers exposed to risk of lead absorption. Some minor points, however, call for comment.

It is stated that "under the present regulations cases without clinical symptoms cannot be notified as lead poisoning." But why not? As is stated, it is Section 66 of the 1937 Factory Act (not a regulation under the Act) which makes lead poisoning notifiable, but there is no direction, specific or implied, which makes it necessary for clinical symptoms to be present before a diagnosis, with subsequent notification, is made. The operative word is "believes," and, if any practitioner believes that punctate basophilia and/or a lowered haemoglobin percentage, etc., in the absence of symptoms or other signs is of a degree to indicate lead absorption in the circumstances prevailing, then it is evidence of "poisoning" and notification should be made. Only in this way can the purpose of notification be fulfilled—i.e., the direction of attention to processes where faulty techniques and practices are leading to lead poisoning. Notification as unfit is irrelevant in this context, but not so if certification is being made for purposes of industrial injury benefit under the National Insurance Act, which prescribes lead poisoning as qualifying for the payment of industrial disease benefit.

Toxic anaemia offers an alternative means of notification, although it is not defined in the regulation (S.R. & O. No. 196 of 1942) making it notifiable. The definition "any dyshaemopoietic disturbance" needs further qualification to take account of the necessary exogenous causative factor, be it lead, benzene, ionizing radiation, or other toxin.

Workers in Group A are stated to have been provided—by regulation—with an extra daily milk allowance. No such regulation now exists, as it was with the introduction of the Pottery (Health and Welfare) Regulations, 1950, that the only remaining regulation requiring the provision of milk was repealed (Pottery Regulations, 1913, S.R. & O. No. 2, 1913). Extra milk cannot be regarded as being effective in *preventing* gross lead absorption, but only possibly in lessening its effects. The provision of milk, indeed, may well lead to a sense of false security and the taking of risks which are not justified where the possibility of lead absorption exists.—I am, etc.,

London, N.W.11. A. W. GILKS.

Allergy and A.C.T.H.

SIR,—Professor G. W. Pickering (June 7, p. 1207) states that, although there is some evidence of altered tissue reactivity to certain specific antigens in acute nephritis, the evidence concerning the role of allergy in this disease is dangerously thin. Bell, in his book on nephritis, sums up the arguments on this issue, and concludes that acute nephritis is not associated with an allergic disturbance. The description of a case with a diagnosis of acute nephritis associated with painful swellings of the phalangeal joints of both hands, and a quick response to treatment with "antistin," may therefore be of interest.

A woman aged 30 attended the surgery complaining of puffiness of the face and swelling of the legs, and this had been noticed for about two days. Albuminuria was found on examination. She was examined in more detail at home the following day.

She now complained of headache, scanty urine, and painful swellings of the small joints of all the fingers, in addition to the swelling of the face and legs.

There was a swelling of the face, and a definite oedema of both legs. The B.P. was 140/95 mm. Hg, which was considered to be on the high side for this patient; the retinae showed no abnormalities; albuminuria was present but not heavy; granular casts were noted. In addition a swelling of the phalangeal joints of both hands was observed. The swelling of the face and legs was in no way indicative of urticaria or angioneurotic oedema and there was no pruritus. There was no recent history of an infective or other condition, and no past history of any kidney disease.

The treatment prescribed was rest, restricted fluid intake, a vegetarian diet, and an antistin tablet three times a day. In about four days the swelling of the face and legs, the albuminuria, and the joint disturbance had subsided. The B.P. was lower, and the patient stated she was quite fit again. The antistin was continued for a further week. It was considered that this patient had an acute nephritis associated with an allergic manifestation in the joints. In view of the quick response of the whole condition to the antihistamine, it is suggested that the kidney disturbance was of an allergic nature.

Professor Pickering in his article divides the allergic tissue responses into two broad types: the response that is immediate and associated with the release of histamine, and the delayed response which is of an inflammatory nature. It is possible that the case described may be of the type associated with the release of histamine, as shown by the quick response to the antihistamine, and that the typical case of type 1 nephritis is associated with a delayed tissue response of an inflammatory nature, and not amenable, as Professor Pickering points out, to antihistamine treatment. The suggestion is therefore made of two broad types of acute nephritis, and this may account for the divergent opinions as to the value of antihistamines in the treatment of acute nephritis.—I am, etc.,

Manchester. JACK CARR.

Trapping the Surgeon's Sweat

SIR,—In your issue of May 31 (p. 1197) I saw a picture of a cap for trapping surgeon's sweat. As a dental surgeon who works in a temperature varying between 75° F. (24° C.) and 90° F. (32° C.) I have had trouble with a sweating forehead and dewy glasses. I devised a headband which I find very useful, as well as being cheap and easy to make. A linen band about two to three inches (5–7.5 cm.) wide, and extending on each side just beyond the margin of the forehead, is used, and on the inner side two flaps are stitched which just overlap along the middle line. On the outer side

another piece of linen is stitched to provide a slot the whole length of the band for a piece of white garter elastic, which fastens at the back of the head with a press stud. The space between the flaps and the main band is occupied by two pieces of fine sponge rubber, sold at the drug stores for applying make-up. These sponge-pads are circular, and I cut one in half and use one over each eye. Before carrying the band to position it is immersed in a little ice water and squeezed out. This ensures a cool dry forehead for some time and the sponge will absorb any sweat. The elastic band and sponge can be easily transferred from one band to another.—I am, etc.,

Nassau, Bahamas. NORMAN STRATON.

Accidental Generalized Vaccinia

SIR,—After the article on "A Case of Accidental Generalized Vaccinia" by Drs. O. A. Finn, J. C. Dick, and J. S. Stevenson (May 17, p. 1067) and subsequent correspondence on the subject, perhaps the following case may be of interest.

The patient was a girl of 6 months who had suffered from a mild degree of eczema since the age of 6 weeks, when weaned on to the bottle: there was a strong familial history of eczema on the paternal side. On June 9 her mother was vaccinated for the first time, before leaving for the U.S.A., and one week later developed a blister on the site, which duly became pustular. Eleven days after this the baby developed a vesicular rash over the eczematous areas on the upper chest and arms. On admission three days later, July 1, the baby was febrile (temperature 103° F. (39.4° C.)) and had a profuse papulo-vesicular eruption smothering the face, neck, upper chest, and upper arms. There were scattered lesions on the limbs and lower trunk: the scalp was clear. She had been vomiting after feeds for two days, but did not appear dehydrated. No abnormality was detected in the other systems.

She was put on to three-hourly feeds of glucose saline, with "elixir benadryl" 1 dr. (3.5 ml.) four-hourly, phenobarbitone ¼ gr. (8 mg.) thrice daily to minimize the risk of convulsions, and soluble penicillin 250,000 units b.d. Proflavine in pareolin 1:1,000 was applied locally to the lesions. The vomiting stopped immediately, and two days later feeds with half-cream National dried milk were recommenced. However, the lesions became very confluent, umbilicated, and pustular, and started to ulcerate in places: this was one week after the onset. In view of the history and character of the lesions, some convalescent vaccinial serum was obtained and two doses were given over a period of two days. The temperature remained at 103° to 104° F. (39.4° to 40° C.). On July 6 her condition deteriorated: she began to twitch, and became cyanosed. Oxygen was administered, and also syrup of chloral, and she improved considerably. However, the next day her temperature suddenly dropped to 95° F. (35° C.), and during the evening she died. Swabs taken on admission revealed on culture a growth of *Staphylococcus aureus*, β-haemolytic streptococci, proteus, and pyocyaneus.

I feel that this is worthy of note, and serves as a further warning against allowing eczematous children to come into contact with active vaccination sores. I am grateful to Dr. Warin for his help, and to Dr. Alice Carleton for her advice and permission to submit this.—I am, etc.,

Oxford. MARY L. ASSINDER.

Gall-stone Colic

SIR,—As mentioned in the factual article by Drs. T. R. Littler and G. Ronald Ellis (April 19, p. 842), gall-stone colic may occur only at night. Patients I have seen with this pain pattern have had stones which are single and the size and shape of a green pea. They have also been heavy, and though they were not analysed I guessed they contained a good deal of calcium.

When the patient is erect the fundus is the lowest part of the gall-bladder and the stone lies there quietly; when, however, the patient lies on her back, the stone after some time may gravitate into Hartmann's pouch, which is now the lowest part of the gall-bladder, and may thus cause biliary colic by blocking the entry of bile into the cystic duct.—I am, etc.,

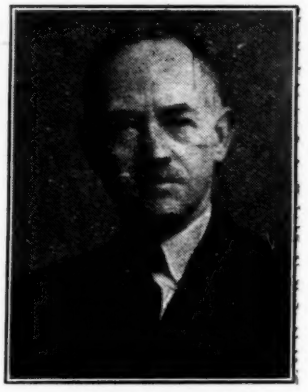
Sydney. T. MAYNARD FURBER.

Obituary

Sir JACK DRUMMOND, D.Sc., F.R.S.

The civilized world has been shocked by the brutal murder of Sir Jack Drummond and his wife and daughter while on holiday in France on August 5. His death is a grievous loss to British medical science and to biochemistry.

Jack Cecil Drummond was born on January 12, 1891, and was educated in the University of London, first at Queen Mary College and then at King's College. Originally studying chemistry, he was quick to realize the growing importance of the new subject of biochemistry, and became a research assistant in biochemistry at King's College, London, in 1913, under Dr. Otto Rosenheim, F.R.S. Here he made his mark as an investigator, and in 1914 was appointed research assistant in the Biochemical Department of the Cancer Hospital Research Institute, London, of which institution he became Director of Biochemical Research in 1918. To his lasting regret he was considered unfit to serve in an active capacity in the war of 1914–18, but he threw his energies into nutritional research, a matter of clear relevance to the problems which faced the country in its war effort. At this time Casimir Funk was investigating the nature of the substance, present in rice polishings, which was capable of curing the polyneuritis developing in pigeons fed on a diet of polished rice, and Drummond entered with zest and vigour the field of vitamin biochemistry as assistant to Funk. The reputation he established as the result of his researches in the field of the vitamins led to his appointment as reader in physiological chemistry at University College, London, in 1919, under the late Professor E. H. Starling, F.R.S. Here he continued his researches on vitamins, and was made the first professor of biochemistry at University College, London, in 1922, at the early age of 31. At University College his investigations on vitaman-B deficiency and its relationship to inanition, and also on the nature of substances having vitamin-A and vitamin-D activity, quickly established him as an international authority on the subject of accessory food factors. He it was who advocated dropping the final "e" of "vitamine" (the name coined by Funk) so that the resulting word "vitamin" should be acceptable under the Chemical Society's standard scheme of nomenclature (*Biochemical Journal*, 1920, **14**, 660).



[*Walter Stoneman, London.*

His conspicuous ability to convey to lay audiences the significance of the technical aspects of nutrition and the role played by vitamins in health and disease led to his being called to advise many bodies concerned with problems of a practical nature in nutrition; for example, he visited Newfoundland in 1931 to report on the steps needed to alleviate the malnutrition which at that time was not uncommon in the island. In 1933 he was invited

by Stanford University, California, to give the Lane Lectures on the subject of nutrition, and also was Harvey Lecturer in New York in the same year.

In 1939 he published with Anne Wilbraham the famous book *The Englishman's Food*, a volume which combines in a delightful way an erudite knowledge of nutrition in its scientific aspects with that interest in history and in the sociological significance of nutritional problems in which Drummond delighted. It was his co-author in this work whom he married in 1940.

When the war of 1939–45 came, his services were quickly utilized by the Ministry of Food, and he soon became Chief Scientific Adviser to the Ministry. In this capacity, particularly in association with Lord Woolton and Lord Horder, Drummond was able to display to the full those outstanding abilities which he had already shown in dealing with general nutritional problems. His ability to express scientific findings in words easily understood by the layman was now of national importance, as also was his capacity to get on with all classes of men. The problems in nutrition with which he had to deal at short notice and with little preparation were large in number and sometimes of vital importance to the country, and the strain of working as Drummond worked would have overwhelmed a man with less vitality and stamina. But he never lost the boyish vigour and breezy and approachable manner which characterized him from the earliest days; and during the darkest period of the war, at a time when the Ministry of Food was naturally subject to much criticism, he dealt quickly and firmly with a host of day-to-day problems, while at the same time advising the Minister wisely and effectively on matters of long-term policy. Thus he had to work out, with imports limited and sometimes uncertain, how essential and sustaining nutrients could best be supplied to the nation from what was available. In doing this he not only helped successfully to overcome the immense difficulties which faced the Ministry of Food but also assisted in the introduction of developments of lasting nutritional and sociological significance, such as the provision of free vitamins and the almost complete elimination of rickets among children.

In 1944 he became adviser on nutrition to the Allied Post-war Requirements Bureau and of S.H.A.E.F., and later was appointed adviser on nutrition for the control commissions for Germany and Austria (British Element). He entered German-occupied Holland before hostilities had finished, in order to advise on the procedures needed to relieve the starving Dutch people with the minimum possible delay, and not only did he speedily bring succour to the starving but also ensured that the unrivalled opportunities for the investigation of scientific aspects of starvation thus presented should not go unattended. His war services were recognized by the conferment on him of the U.S. Medal of Freedom with Silver Palms; he was made a Commander of the Order of Orange Nassau; the University of Paris conferred on him the degree of Doctor *honoris causa*. Already in 1944 he had been knighted and had been elected a Fellow of the Royal Society.

His influence on the development of medical science does not rest only on his personal contributions. He founded a flourishing school of biochemistry at University College, London, and his pupils, whom he inspired with his own enthusiasm and zeal, have held many important posts in this country and abroad, including five chairs of biochemistry in Great Britain.

It was a matter of some surprise to many who knew him when, in 1945, Drummond resigned the post of professor at University College, which he had held *in absentia* during the war period, and became director of research to Boots Pure Drug Company. Here, however, his talents had wide opportunity for employment, and he entered into his new duties with the zest of a man many years his junior. Despite a serious illness early this year he had made a complete recovery and had returned to work in a remarkably short time.

The whole country benefited from his nutritional wisdom, but the young subject of biochemistry in particular received a stimulus from his energy and guidance during its formative years which no other man could have given, and to those who were privileged to know him as friend and teacher his memory will remain green for ever.

Lord HORDER writes: The shock of Jack Drummond's death, and the nature of it, make a cool assessment of his value to the community and to his friends quite impossible at this moment. But a few thoughts and memories ask for expression in response to the Editor's invitation. It has been said that opportunity finds the man who is prepared for it. It was so with Drummond when Lord Woolton chose him as his scientific adviser in 1939. No other man in the country was so fit for this key position. His work on vitamins (he was author of the name "vitamin C," later known as ascorbic acid) and upon various aspects of nutrition were probably no less responsible for the choice than his authoritative yet fascinating book on *The Englishman's Food*, a work of science and of erudition which is likely to remain a classic for all time. In his post Drummond made one of the greatest contributions to Britain's ultimate victory in the war of any of those working towards this end. He was backed by a Minister who believed in the expert, taking the utmost of the latter's advice that was administratively possible.

My own first acquaintance with Drummond was when he was Director of Research at the Cancer Hospital. At the time of his appointment to the Ministry of Food I was asked to advise the Minister on the general health aspects of war-time feeding. For the next six years I saw much of my co-adviser, working together with him in most complete harmony, and with a chief in whom we both had complete confidence.

Not himself a medical man, and well known to have been severe in his criticism of doctors in their neglect of the scientific aspects of diet, both in the teaching of students and in practice, Drummond might well have proved hard to work with. But his tolerance, his humility, and his insatiable desire for the truth never failed him, and he was for this reason the ideal colleague. No praise is too great for his patient endurance of the legion of inquirers who came to him and of the many who brought their (to them) certain dietetic panaceas, while his tenacity in respect of his job was a stimulus to us all.

He was also the ideal husband, father, and friend. To have been admitted to the intimacy of his family and his home was as great a privilege as to have shared in the same task.

A medical friend writes: All who knew Drummond must still feel stunned by the news of the brutal and senseless murder of himself, his wife, and his daughter. Drummond's fearlessness and vitality were wrapped up in a friendliness that disarmed anyone whom he criticized—and doctors were at times a target for his witty shafts of criticism directed at their, to him, lack of knowledge of nutrition. I remember well visiting him at the Ministry of Food in the early years of the war, and the enthusiasm with which he explained his plans, plans which aimed really at changing the food habits of people who were liable to go off the proper nutritional track. His approach was, however, essentially empirical, and if something did not work out as he thought it would

he would quickly change his tactics. Apart from the economic aspect, Drummond wanted to seize the opportunity offered by the war of attacking dietetic ignorance. The knowledge was there. People should use it—and so should the medical profession. Before the war Drummond was critical of the low salaries paid to whole-time professors of the basic sciences. He said to me on one occasion that if these salaries were not made more attractive the pharmaceutical industry would capture the best biochemists to the detriment of the universities and the medical schools. So it was not altogether surprising that after the war he did not return to academic life but accepted the post offered to him by Boots Pure Drug Company.

E. R. GARNETT PASSE, F.R.C.S., F.A.C.S., D.L.O.

Mr. Garnett Passe, who died suddenly on holiday in Truro on August 1, at the untimely age of 48, had become one of the best-known aural surgeons in London and had gained an international reputation as a most accomplished technician in the surgery of the labyrinth. Only last month, at the Annual Meeting of the British Medical Association in Dublin, he took a leading part in the discussion on Ménière's syndrome, and mentioned that in the past six years he had performed over 200 sympathectomies, with encouraging results.

Edward Roland Garnett Passe was born in Johannesburg, but left for Australia at an early age, and went to school and subsequently to medical school in Melbourne. He qualified there in dentistry in 1926, and then came over to the London Hospital in order to obtain a medical qualification, taking the M.R.C.S., L.R.C.P. in 1929. At the London Hospital he became fascinated with the problems of oto-laryngology and worked as house-surgeon and first assistant with Norman Patterson, Geoffrey Carte, and Mr. Donald Wheeler; he was also house-surgeon at the Central London Hospital, Grays' Inn Road. He took the D.L.O. in 1931, the F.R.C.S. in 1936, and the Fellowship of the American College of Surgeons in 1945. A turning-point in his life came in 1937, when he studied at Gunnar Holmgren's clinic in Stockholm and met there Julius Lempert, of New York. Holmgren was then engaged in his endeavours to solve the difficulties of fenestration of the labyrinth in order to relieve deafness in otosclerosis, an operation which was afterwards elaborated and streamlined by Lempert. Garnett Passe became the pioneer of the fenestration operation in England, and in 1939 published in the *Journal of Laryngology and Otology* a series of 14 cases, the first dozen according to Holmgren's technique and the last two according to that of Lempert; five of the cases showed improvement in hearing. To the orthodox otologist at that time the suggestion of treating deafness by surgery was anathema, if not something worse, and it is probable that if Garnett Passe had never done a fenestration he would have been elected to the staff of the London Hospital as an able otolaryngologist interested mainly in the larynx, for about this time he published a small book on *The Singing Voice*, and he inherited a large connexion among singers and actors from the late Geoffrey Carte, with whom he worked. But the die was cast, and Garnett Passe went on to perform over a thousand fenestrations and to become more and more interested in sympathectomy for the relief of tinnitus and nerve deafness as well as Ménière's disease. Five years ago he was invited over to Utrecht to demonstrate the fenestration operation to Dutch otologists, and three years ago to Cairo to demonstrate it to Egyptian surgeons. He was aural surgeon to King Edward Memorial Hospital, Ealing, and to the Wembley Hospital, but, to the widely expressed regret of many of his colleagues, he was never elected to a teaching hospital. For 20 years he was an enthusiastic member of the R.N.V.R., and received the V.R.D.; during the war he was surgeon-commander, R.N.V.R., and, being fortunate enough to be stationed at Bermuda, was able when on leave to visit Lempert's clinic in New York on several occasions.

Passe's operation was, at first, stellate ganglionectomy, coupled with the stripping, ligation, and division of the vertebral artery; but in 1951 he substituted preganglionic section of the second and third thoracic ganglia and division of the sympathetic trunk below the third thoracic ganglion. The encouraging results of this operation aroused much interest among otologists at home and abroad. Garnett Passe read a paper on it at the Fourth International Congress of Otolaryngology in London in 1949, gave a report on 110 cases at the Royal Society of Medicine in August, 1951, and published articles on the subject in *Acta Otolaryngologica* (1952) and in this *Journal* (1948). He was invited to read a paper at the Latin-American Congress of Otolaryngology at Sao Paulo in 1951, and thereafter received an honorary degree at Rio de Janeiro. He had been invited to Boston next November by the New England Otolaryngological Society, to open a discussion on sympathectomy, to be followed by Dr. Reginald Smithwick. Much of his fundamental research work was carried out at the Ferens Institute in association with Dr. J. S. Seymour.

Garnett Passe had been an all-round sportsman in his youth, played down to a handicap of 8 at golf, and was proud and happy to have gained a silver medal for ski-ing at Davos at the age of 47. But he had been haunted by ill-health and particularly a high blood pressure for many years. He had been interested in sculpture before the war, and after being warned earlier this year to take things more quietly he took up sculpture seriously, and during his last holiday spent much of his time working happily with Barbara Hepworth in Cornwall. Short and dapper, with iron-grey hair, Garnett Passe had worked hard all his life, and he continued to do so until the end. He was one of the kindest, most even-tempered and generous of men, and his numerous patients all became his friends. Nothing was too much trouble for him, and he liked to do all his own post-operative dressings and after-treatment. He had no children, and his married life was of the most serene; his patients, friends, and colleagues would express to his widow deep sympathy in her tragic and unexpected loss.—R. S. S.

Dr. S. Leonard Simpson writes: From his early days Garnett Passe was intense, resolute, and tireless in the pursuit of deeper knowledge of his subject and the perfection of surgical technique. He did not readily accept conventional ideas, particularly when they were therapeutically negativistic, and he undertook and initiated avenues of surgery which required courage and skill and which were to remain in dispute for some years before receiving general or qualified acceptance. His deep compassion and desire to alleviate human suffering was a large factor in determining a course of action which was bound to be uphill all the way. Although a firm believer in his own achievements and considered conclusions, he was nevertheless innately modest. The fact that he did not secure appointment to the consulting staff of his student hospital might well have been an additional spur to efforts to achieve wider recognition, and there is no doubt that in recent years this came to him in full measure. As recently as July 15 Garnett

Passe received a letter from Dr. Leighton F. Johnson, president of the New England Otolaryngological Society, inviting him to be principal speaker at the next meeting of the society on "Surgery of the Sympathetic in Relation to Neurovascular Lesions of the Internal Ear (including Ménière's Disease)."

In accepting the invitation Garnett Passe expressed great pleasure that Dr. Reginald Smithwick, an eminent authority on sympathetic nerve surgery, was to discuss the paper. Passe had recently given papers on this in otosclerosis and related subjects to the Royal Society of Medicine and to this year's Annual Meeting of the B.M.A. in Dublin, and was speaking next year at an international congress to be held in Holland: in fact, he had arrived at the full tide of his technical and intellectual eminence. His patients learned to know him for his great kindness, understanding, humanity, and infinite care, particularly in the post-operative dressings, which he carried out himself both for private and hospital patients.

In his home he was a perfect host, full of quiet but witty and stimulating conversation and with a wide knowledge of the world, in which he had travelled greatly. He was also an excellent and sympathetic listener. On the golf course he played with zest and intensity and achieved many successes. He will certainly be missed from the annual meetings of the Medical Golfing Society and from the Wentworth and Sunningdale clubs, where he was so much liked and respected. As recently as February this year I met him ski-ing with his wife and some friends at Davos, and he then went on, perhaps rather recklessly, to do some more difficult ski-ing at Zermatt. My last vivid remembrance of him is that of some two months ago playing a round of golf with another Australian, Norman Von Nida, and expressing almost boyish delight in the acquirement of a new golf technique which lengthened his drive and increased his accuracy. This was characteristic not only of his perpetually youthful outlook, but also of his irresistible urge towards perfection in anything he undertook. He showed great skill in drawing and in sculpture, and characteristically during the last two weeks of his life when on holiday in Cornwall he worked in the studio of a well-known sculptress, and there learned how to work in stone. He also made a model of a head in clay, and the view was expressed that in this field, too, he showed exceptional ability and potentiality.

These observations would be incomplete if I did not add a word in regard to the perfect harmony and understanding between Garnett Passe and his wife, Barbara, over the many years of their very happy life together. She shared his interest in his work and in ski-ing and golf, and he always spoke of her as an ideal helpmate and partner. Our deepest sympathy goes out to her in her bereavement.

HAROLD ETTRICK MOORE, O.B.E., M.B., Ch.B.

Dr. Harold Ettrick Moore, who died on August 6, aged 73, at his home at Crewe, was one of the outstanding pioneers in rehabilitation of the injured industrial worker.

Moore entered Owens College, Manchester, in 1899, and found himself a member of a vigorous generation in the Manchester Medical School which produced two future Presidents of Royal Colleges—Lord Webb-Johnson and Sir William Fletcher Shaw. As an undergraduate Moore's personal qualities gained for him a wide circle of friends and admirers among the students of all faculties. He was a fine athlete. He captained the college rugger side and played for Lancashire; he also captained the Victoria University cricket team drawn from the three constituent colleges in Manchester, Liverpool, and Leeds. Graduating M.B., Ch.B. in 1904, he held the post of house-surgeon at the Manchester Royal Infirmary for six months before entering general practice. After the war of 1914–18 his old chief, Sir William Thorburn, then consulting surgeon to the London, Midland, and Scottish Railway Company, persuaded him to abandon general practice and to take charge of the small railway hospital at Crewe.

In this new career Moore was to achieve great distinction. His routine duties were to examine recruits to the railway service, to treat minor injuries among the employees, and to give evidence in the county courts in compensation cases. The last experience soon directed his mind to the need for the provision of better facilities for the rehabilitation of injured men, who, after discharge from hospitals or from the care of their general practitioners, had been left to work out their own salvation. At the railway hospital in Crewe, Moore established a rehabilitation centre with very simple equipment. The hospital, apart from its out-patient casualty department, was little more than a hostel with a large gymnasium. The keynote of the day's programme was activity. Under Moore's inspiring guidance the men admitted to the railway hospital regained the urge to exhibit their old industrial vigour. Moore's work in this important field of social medicine gradually became known far and wide, and both the British Medical Association's Report on Fractures (1935) and the report of the interdepartmental committee of the Home Office, the Ministry of Health, and the Scottish Office on the rehabilitation of persons injured by accidents (1937) bore the mark of his influence. During the second world war he was appointed adviser in rehabilitation both to the Royal Air Force and to the Royal Navy, and his invaluable national services were somewhat inadequately recognized by appointment as O.B.E. in 1945. Before his recent retirement from the medical service of British Railways, Moore had the satisfaction of enjoying for a short time the title of principal medical officer. "H.E.," as he was known to his many friends, looked and spoke like a man of distinction, as indeed he was; but one of his most attractive qualities was his modesty.

Dr. T. S. HARRISON writes: Dr. H. E. Moore came to the Medical School of the newly created Manchester University in the late nineties. Slim, but of great spirit, he grew into the very tough and wiry rugby forward who was for several years on the Lancashire side and gained his North cap. Clever with hands and feet, he was never far from the ball or the front row of the scrum, in the days when that was the mark of a good forward. He captained the university side and the mixed Manchester, Liverpool, and Leeds University sides which took on the Lancashire, Yorkshire, and Cheshire counties. His cricket was also distinguished, for he captained the university side, being a sound wicket-keeper who stood up to any bowling, and he had a left-hander's beautifully timed off-drives. In later life his golf was carefree, and he played to a handicap of about four.

The qualities of all-out spirited effort which he brought to his games he carried to his work, as was duly noted by Sir William Thorburn in his house-surgeon, and in the offer of the L. and N.W. medical officer's work at Crewe. Moore at this time—1922—was in the toils of monotony as a D.C.M.S. in the Ministry of Pensions in Newcastle-upon-Tyne. In the orthopaedic work which distinguished his 30 years at Crewe and made him so useful in rehabilitation in the last war he showed the same spirited, right-thinking endeavour which had placed him among the last to leave Gallipoli in the first world war, where he had been surgeon in the tented hospital on Cape Helles. Again, he was among the last to leave the hospital ship *Asturias* when torpedoed, searching along flooded alleyways for possibly injured staff, and was then in the final event of the war, the closing campaign in Italy.

He could estimate fairly the physical obstructions to restoration of function, and if he considered these could be overcome there was no limit to the sensitive understanding which brought his patient from lethargy and "light duty" to a patient and persistent co-operation in restorative measures and to full work and pay.

It is recorded of a soldier, "There is no need to record his virtues: they are engraven in the hearts of his friends." All who had been associated with him were Moore's friends, and railwaymen of all grades were round his grave on Saturday. Cloud and shadow were in plenty in his 72 years, but, storm or shine, "H. E." could be relied on to play the game and seek no other reward.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

The Nuffield Foundation has offered grants of £1,000 a year for two years for work on peptides of adrenocorticotropic hormones under the supervision of Professor A. R. Todd; of £4,100 spread over two years for work on these hormones under the supervision of Professor F. G. Young; and £2,400 spread over three years in support of an investigation in the Department of Colloid Science on antigen–antibody reactions, all of which the Council of the Senate has gratefully accepted.

J. F. R. Withycombe, M.Chir., F.R.C.S., has been elected to a Comyns Berkeley Bye-Fellowship at Gonville and Caius College.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on July 31 with the President, Sir Cecil Wakeley, in the chair, Dr. O. C. Carter and Dr. Bernard Johnson were admitted to the Council. A resolution of condolence was passed on the death of Sir Hugh Cairns, a past member of the Council.

Professor F. Wood Jones was appointed to the post of Honorary Curator of the Hunterian collection of human and comparative anatomy on his retirement from the Sir William Collins Professorship of Anatomy.

Mr. Hedley Whyte was reappointed as representative of the College on the council of King's College, Newcastle-upon-Tyne, and Mr. L. E. C. Norbury on the examination and tuition advisory board of the Association of Medical Records Officers.

Dr. B. E. Heard (St. Mary's Hospital) was appointed Lecturer in Pathology. The Hallett Prize was awarded to Dr. James Keith Ross (Middlesex Hospital).

It was decided that as from January 1, 1954, the period of post-graduate surgical training in recognized posts required of candidates for the final Fellowship examination be increased to two years.

Diplomas of Fellowship were granted to D. I. Stirk (St. Mary's) and G. Westbury (Westminster).

Diplomas of Membership of the College were granted to the candidates whose names are printed in the *Journal* of August 9 (p. 345) in the report of the meeting of the Royal College of Physicians of London as recipients of the L.R.C.P.

Diplomas in Public Health, in Ophthalmology, and in Industrial Health were granted, jointly with the Royal College of Physicians of London, to the candidates whose names are printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of August 9 (p. 345).

The Council received with gratitude a delineascope, the gift of Dr. Howard Naffziger, Hon.F.R.C.S., of San Francisco.

ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

At the annual meeting of the College held at Adelaide in May, with the President, Dr. Alex Murphy, in the chair, the following Members were elected to the Fellowship of the College: C. G. Bayliss, J. H. Colebatch, K. J. Grice, W. E. King.

The following candidates, having satisfied the Boards of Censors in Australia and New Zealand, were admitted to Membership of the College: J. L. Allsop, A. L. Anderson, G. E. Bauer, D. A. Ballantyne, B. P. Billington, J. V. Cable, R. G. Dreadon, A. A. Ferris, J. J. Fitzwater, A. J. Goble, C. Gresson, P. F. Hall, D. A. Henderson, K. H. Holdgate, C. W. Howden, J. D. Hunter, I. R. Mackay, T. G. Maddison, J. W. Perry, D. W. Piper, V. E. Sampson, G. Selby, B. C. Sinclair-Smith, I. D. Thomas, A. R. Tink, D. Tomlinson, A. S. Turner, R. H. Vines, C. E. Watson.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 26** (No. 30) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	21	0	6	1		36	2	8	1	2
Dysentery	135	19	45	0	1	226	26	59	1	
Encephalitis, acute	5	0	0	0		11	0	0	0	
Enteric fever:										
Typhoid	5	0	2	0	2	61	6	1 (B)	1	
Paratyphoid	75	1	0	0						
Food-poisoning	231	17		0		201	33		2	
Infective enteritis or diarrhoea under 2 years				14	23				24	39
Measles*	7,363	844	96	128	193	5,258	114	123	161	130
Meningococcal infection	34	4	9	1		35	3	19	1	
Ophthalmia neonatorum	39	5	9	0		27	0	9	0	
Pneumonia†	247	10	142	4	1	308	11	106	2	
Poliomyelitis, acute:										
Paralytic	157	23	9	6	1	50	4	8	5	1
Non-paralytic	96	10				71	3			
Puerperal fever§	260	31	14	2	1	114	9	14	0	
Scarlet fever	1,173	113	144	16	53	758	76	108	19	34
Tuberculosis:										
Respiratory			121	32				144	33	
Non-respiratory			23	10				28	13	
Whooping-cough	2,040	97	91	70	133	3,261	171	266	57	71

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	1		0		*0*	0	*0*	0	0
Dysentery	0	0					1		1	
Encephalitis, acute		0					0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	7		2	0		*12*		*1*	0	0
Influenza	6	0	2	0		*3*	0	*0*	0	0
Measles		0		0			0	*0*	0	0
Meningococcal infection		1	1				0	*0*		
Pneumonia	129	21		10		*86*	7	*0*	6	3
Poliomyelitis, acute	6	3				*4*	1			0
Scarlet fever		0		0			0	*0*	0	0
Tuberculosis:										
Respiratory	83	8	16	3		*106*	12	*15*	2	5
Non-respiratory		2	1	0			1	*4*	2	1
Whooping-cough	0	0		0		*2*	0	*0*	0	2
Deaths 0–1 year	204	23	15	10		*165*	16	*27*	5	16
Deaths (excluding stillbirths)	4,177	609	523	96		*3,839*	557	*465*	92	131
LIVE BIRTHS	7,310	1090	898	244		*6,893*	1152	*872*	229	467
STILLBIRTHS	177	19	29			*191*	22	*27*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Poliomyelitis

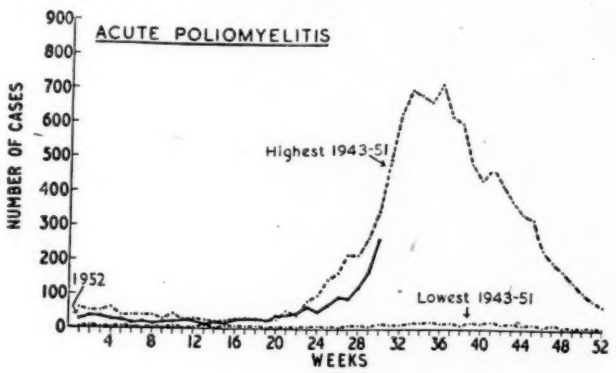
Poliomyelitis notifications in the week ending August 2 (31st week of the year) were as follows: paralytic, 139 (157); non-paralytic, 91 (96); total, 230 (253). This is a decrease of 23 compared with the previous week, the figures for which are in parentheses.

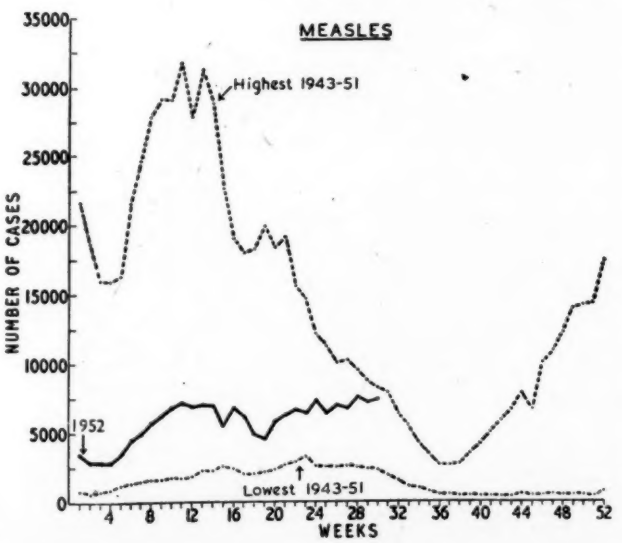
The Table below shows the numbers of notifications in regions and the incidence per 100,000 population for the week ending August 2.

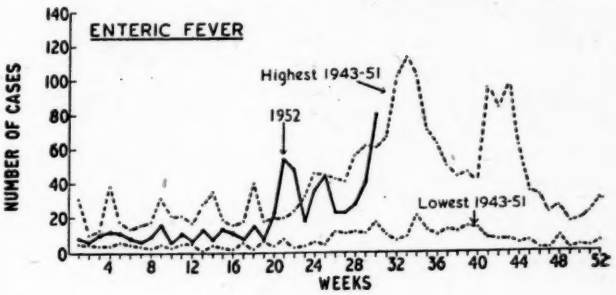
Region	Cases			Incidence per 100,000
	Paralytic	Non-paralytic	Total	
Northern ..	147	138	285	8·39
E. & W. Ridings	139	28	167	4·00
North-Western	101	34	135	2·09
North Midland	25	39	64	1·85
Midland ..	105	46	151	3·41
Southern ..	71	41	112	4·22
South-Western	67	51	118	3·92
Eastern ..	82	54	136	4·43
London & S.E.	294	119	413	3·8
England & Wales	1,088	571	1,659	3·8

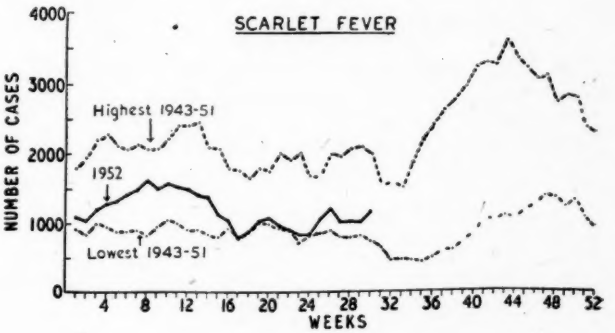
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus - - - - - - -, the figures for 1952 thus ———. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

In England and Wales during the week ending July 26 an increase was recorded in the number of notifications of measles 138, scarlet fever 135, acute poliomyelitis 90, and paratyphoid fever 36, and a decrease was reported for whooping-cough 166.

The largest increases in the number of notifications of measles were London 114, Essex 88, and Lancashire 83. Only small variations were reported in the local trends of scarlet fever. The largest fluctuation in the local trends of whooping-cough was a decrease of 47 in Surrey. The notifications of diphtheria were 4 fewer than in the preceding week; 4 of the 21 cases of diphtheria were notified in Birmingham C.B.

The increase in the incidence of paratyphoid fever was contributed by Wales, where the notifications were 36 more than in the preceding week. The chief centres of infection were Brecknock, Ystradgynlais R.D. 12, and Glamorganshire, Pontardawe R.D. 21.

The number of notifications of acute poliomyelitis were 53 for paralytic cases and 37 for non-paralytic cases more than in the preceding week. The largest returns were London 33 (Wandsworth 7 and the remaining cases distributed over 16 boroughs), Yorkshire West Riding 22 (Leeds C.B. 12), Durham 21 (Felling U.D. 5), Essex 20 (Southend-on-Sea C.B. 6), Northumberland 17 (Newcastle-upon-Tyne C.B. 11), Middlesex 13 (Ealing M.B. 4), Kent 12, and Surrey 11.

The largest returns of dysentery were Yorkshire West Riding 38 (Leeds C.B. 10, Holmfirth U.D. 14), London 19, and Lancashire 19.

Comparability of Statistics

The W.H.O. Centre for Classification of Diseases has prepared a booklet entitled *Comparability of Statistics of Causes of Death according to the Fifth and Sixth Revisions of the International List* (2s. 9d.), to indicate difficulties in maintaining continuity of statistics and how they may be overcome. Rearrangements of the International List and changes in the form of death certificate, together with the diversity in the principles by which the principal cause of death was selected for tabulation from several causes stated on the certificate, have all contributed to making comparability increasingly difficult. These problems are partly illustrated in a section on diabetes statistics, where it is shown how the rigid rules employed in the past for selecting the

principal cause placed undue weight on diabetes as the cause of death. The use of schematic rules resulted in fictitious statistics of diabetes, making them incomparable with the statistics of those countries which relied on the opinion of the certifying physician as to the principal cause of death. Methods of preserving continuity of statistics of mortality rates are discussed and examples of possible situations given. The final 24 pages are devoted to three tables: the first giving the International List categories, sixth revision, expressed in terms of categories of the fifth revision; and the second and third the deaths in Canada in 1949 coded according to the fifth and sixth revisions and grouped according to the Intermediate and Abbreviated lists respectively.

Week Ending August 2

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 997, whooping-cough 2,042, diphtheria 19, measles 7,309, acute poliomyelitis 230, dysentery 93, paratyphoid fever 130, and typhoid fever 5.

Eire Statistics.—In the last two weeks we have been unable to include in the Table of vital statistics the returns from the Republic of Ireland for deaths, live births, and stillbirths in the principal towns there. This is because of a printers' strike in Dublin, which still continues.

Medical News

Half-yearly Indexes.—The half-yearly indexes to Volume I of the *Journal* and the *Supplement* for 1952 are now being sent to readers who receive them regularly. Readers who have not previously asked for them to be sent regularly can obtain copies, post paid, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1; those wishing to receive the indexes regularly as published should mention this.

Annual Report of the Board of Control.—The 38th annual report (H.C.243, H.M.S.O., 4d.), that for 1951, remarks that more mental patients are entering hospital voluntarily, though conditions vary greatly from hospital to hospital throughout the country. While in some less than 10% of patients are certified, in others about 50% of admissions are the result of certification. The report suggests that certification can often be avoided if a patient can meet the psychiatrist before hospital treatment is undertaken, since he may be persuaded to come in of his own accord. This makes his treatment much easier, since he is more co-operative, and avoids the social stigma so disliked by the family. The new out-patient centres, mainly staffed by hospital medical officers, are a help towards this ideal. In 1939 there were about 200 of them, and to-day there are nearly double this number.

Australasian College of Surgeons Prize.—Last year £1,042 was subscribed to provide a prize to recognize the services to the College of Sir Hibbert Alan Stephen Newton, a foundation Fellow and later a president of the College. The Alan Newton Prize is to be awarded biennially.

Candidates for the prize must be Fellows of the Royal Australasian College of Surgeons (not being members of the Council), the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh, the Royal College of Surgeons in Ireland or Fellows in Surgery of the Royal Faculty of Physicians and Surgeons of Glasgow. Essays must be typewritten in English and must not exceed 75,000 words. Case histories of cited cases must not be included in the typescript but placed after it in an appendix. Each essay must be distinguished by a motto and accompanied by a sealed envelope containing the name and address of the author and having on the outside of the envelope the motto corresponding to that on the essay.

The subject for the first essay is "The Pathology and Surgery of Diseases of the Parathyroid Glands." All entries must be in the hands of the secretary on or before December 1, 1954. Full information from the secretary, R.A.C.S., Spring Street, Melbourne, C.1.

Indian Scientific Journals.—Unesco has recently issued a list of scientific periodicals published in India. Of the 226 titles included, 40 deal with medicine (including two from Goa). Title, frequency, and full address are given for each journal. Unesco is preparing similar lists for other countries, and has already issued one for New Zealand. Copies may be obtained gratis on application to the Department of Natural Sciences, Unesco, 19, Avenue Kléber, Paris, 16.

Norbert Wiener, Professor of Mathematics, Massachusetts Institute of Technology, has been awarded the Alvarenga Prize for 1952 by the College of Physicians of Philadelphia for his contribution to the field of cybernetics.

NEW ISSUES

Journal of Clinical Pathology.—The next issue of this journal (Vol. 5, No. 3) will be available in a week's time. The principal contents include:

Primary Epithelial Tumours of the Jaw. T. F. Hewer.
Lower Nephron Nephrosis after Transurethral Resection of the Prostate. John Swinney and B. E. Tomlinson.
Anisotropic Non-silicious Crystalline Inclusions in a Dysgerminoma of Tuberculoid Appearance. R. Eric Potts.
The Histological Changes in Hydantoinate Gingivitis. L. Crome.
The Value of Rib Biopsy in the Study of Marrow Disorders. M. S. R. Hutt, P. Smith, A. E. Clark, and J. L. Pinniger.
Vitamin B_{12} Assay in Body Fluids using Euglena Gracilis. G. I. M. Ross.
The Construction and Clinical Significance of the Coagulahepatogram. W. Rieben.
The Relation between Polyagglutinability of Erythrocytes in vivo and the Hübener-Thomsen-Friedenreich Phenomenon. J. Reepmaker.
Determination of the Unsaturated Iron-binding Capacity of Serum. S. Ventura.
The Application of a Haemagglutination Technique to the Study of Trichomonas Vaginalis Infections. M. G. McEntegart.
The Relationship between Iron Storage and Anaemia. W. M. Davidson and R. F. Jennison.
The Effect of Photo-electric Cell Temperature on Flame Photometer Determinations. A. O. Wilson.
Technical Methods:
- A Rapid Method for Determining Faecal Fat. O. E. Neufeld.
- A Direct Scanning Apparatus for Reading Electrophoretic Paper Strips. L. L. Griffiths.
- A Simple Method for the Aseptic Filling of Screw-capped Containers. J. E. O'Hagan.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

Journal of Neurology, Neurosurgery and Psychiatry.—The next issue of this journal (Vol. 15, No. 3) will be available in a week's time. The principal contents include:

Observations on Partial Removal of the Post-central Gyrus for Pain. Walpole Lewin and C. G. Phillips.
Micturition Reflexes in Man. P. W. Nathan.
Thermal Sensation in the Bladder. P. W. Nathan.
Aspergillus Infections of the Central Nervous System. Subramani Iyer, Philip R. Dodge, and Raymond D. Adams.
The Localization of Aneurin Pyrophosphatase in the Brain. D. Naidoo and O. E. Pratt.
Wounds of the Visual Pathway. II: The Striate Cortex. J. M. K. Spalding.
Dysplasia in Left-handed Patients with Unilateral Brain Lesions. M. E. Humphrey and O. L. Zangwill.
Cerebral Dominance in Cases of Reading Disability. M. McFie.
Electromyographic and Endocrine Studies in Chronic Thyrotoxic Myopathy. K. V. Sanderson and W. R. Adey.
Observations on a Case of Myotonia Paradoxa. John Marshall.

THE VITAL STAINING OF MUSCULAR BIOPSIES WITH METHYLENE-BLUE. C. Coërs.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

These journals are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

Royal Army Medical College.—The College is running a series of evening lectures this winter which are open to all members of the profession, admission free. The first lecture, to be given by Captain M. P. Ward, R.A.M.C., on October 6, at 5 p.m., is called "The Mount Everest Reconnaissance, 1951." Others include "Korean Experiences," by Major J. M. Adam, R.A.M.C., "Children in Hospital," by Professor Alan Moncrieff, "Modern Trends in Hospital Architecture," by Mr. R. Llewelyn Davies, and "Some Aspects of Chemotherapy in Tropical Medicine," by Brigadier J. S. K. Boyd, F.R.S. All lectures will be given in the lecture theatre at the College, Millbank, S.W.1 (entrance from John Islip Street, near the Tate Gallery).

Infantile Paralysis Fellowship in North London.—A group for the promotion of the welfare of people disabled by poliomyelitis in Islington, Stoke Newington, Finsbury, Shoreditch, and the City of London is being organized by Islington Rotary Club, and an inaugural meeting will be held in the Town Hall, Upper Street, N.1, at 7 p.m., on September 22, to which all sufferers and sympathizers are invited. Full information may be obtained from 80, Orpingley Road, N.7.

APPOINTMENTS

BARBER, J. M., M.D., M.R.C.P.Ed., Consultant Physician to North Down Group of Hospitals, Northern Ireland.

BOYD, JOHN MACKIE, M.B., Ch.B., D.P.H., Assistant Medical Officer of Health and Assistant School Medical Officer for Banffshire.

PARQUHAR, ROBERT WARRENDER, M.B., Ch.B., D.P.H., Divisional Medical Officer, Health Division No. 2, Lancashire County Council; Medical Officer of Health Lancaster Borough, Lancaster Rural District, Lunesdale Rural District, and Carnforth Urban District.

GRACE, R. F. T., M.D., M.R.C.P., Assistant (Consultant status), to the Department of Psychological Medicine, the National Hospital, Queen Square, London, W.C.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Dobson.—On July 24, 1952, to Dr. Margaret J. Dobson (formerly Barker), M.B., Ch.B., wife of Sydney F. Dobson, of Marple, Cheshire, a son.

Lord.—On August 7, 1952, at the County Infirmary, Louth, Lincs, to Reda (formerly Williamson), wife of Dr. W. J. H. Lord, a son.

Tempest.—On July 26, 1952, at St. James's Hospital, Leeds, to Jean Elisabeth (formerly Turner), wife of Mr. Michael N. Tempest, F.R.C.S., a daughter.

MARRIAGES

Abernethy—Dennis.—On July 25, 1952, Barclay Chivas Abernethy, M.B., of Aberdeen, to Isobel Ellen Dennis, M.S.R., of Aberdeen.

DEATHS

Anderson.—On August 1, 1952, at Greenacres, Wootton Courtenay, Somerset, Kenneth Anderson, M.B.

Bannister.—On August 5, 1952, at "Morwenna," Lidden, Penzance, Marmaduke Bannister, M.D., formerly of Blackburn, aged 86.

Chase.—On August 6, 1952, at "Oakwood," Brampton, Cumberland, Robert Godwin Chase, M.B., B.Ch., of 68, Victoria Road, Headingley, Leeds.

Dickson.—On August 2, 1952, at Easthook, Bridgnorth, Salop, Louis Edington Dickson, M.D., aged 74.

Grunbaum.—On August 2, 1952, Lionel Nathan Grunbaum, M.B., B.Chir., M.R.C.P., of 78, Clifton Hill, London, N.W.

Henderson.—On July 31, 1952, at The Hawthorns, Coldstream, Berwickshire, John Henderson, M.B., Ch.B.

Lee.—On August 6, 1952, at Storrington, Sussex, Frederick William Lee, M.R.C.S., L.R.C.P., aged 81.

Lee.—On August 9, 1952 at 17, Princes Avenue, Muswell Hill, London, N., William Edward Lee, M.D., F.R.C.S., aged 81.

McWhan.—On August 6, 1952, at Cheeklaw House, Duns, Berwickshire, Andrew Alexander McWhan, M.B., Ch.B., D.P.H.

Marsh.—On August 9, 1952, at Pillmere House, Saltash, Cornwall, Ernest Louis Marsh, M.B., C.M., D.P.H., late of Shanghai, China.

Marwick.—On August 9, 1952, at Edinburgh, Robert Elrick Marwick, M.B., Ch.B., of 7, Learmonth Terrace, Edinburgh.

Moore.—On August 6, 1952, at his home, 1, Wellington Villas, Crewe, Cheshire, Harold Etterick Moore, O.B.E., M.B., Ch.B.

Morris.—On August 2, 1952, John Morris, M.R.C.S., L.R.C.P., of 10, Park Avenue, Newport Pagnell, Bucks, aged 71.

Munro.—On August 4, 1952, at Denham Leys, Quainton, Bucks, John Douglas Ross Munro, M.D., formerly of Nantwich, aged 82.

Passe.—On August 1, 1952, Edward Roland Garnett Passe, F.R.C.S., F.A.C.S., D.L.O., B.D.S., of 36, Weymouth Street, London, W.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Dysentery Carriers

Q.—*What should be done about symptomless bacillary dysentery carriers?*

A.—The dysentery carrier state is usually transient and therefore calls for no active treatment. The subject should simply be instructed in the precautions to be taken to avoid infecting other people. If the stools remain positive, a course of one of the less soluble sulphonamides may be given—for example, succinylsulphathiazole, 4 g. four times daily for one week. Alternatively, streptomycin may be given by the mouth (1 g. four times daily); this drug is not absorbed from the alimentary tract and is therefore quite harmless when so administered. Both of these forms of treatment are expensive and should rarely be necessary. None of the still more expensive newer antibiotics is indicated for treating this condition: owing probably to the nature of their action on bacteria, which is growth-inhibitory rather than lethal, they are not very useful either for preventing the development of the carrier state or for curing it.

Breast Involution after Repeated Childbirth

Q.—*I have a patient who, after the birth of each of her four children, has suffered increasing involution of the breasts. She has now hardly any breast tissue left, and this distresses her considerably. Since increase of breast tissue has been reported in A.C.T.H. treatment, would this be of any value? If not, can anything be done to help her?*

A.—The first question is one of diagnosis. The chief major endocrinological cause for involution of the breasts to a size smaller than that preceding the pregnancy is postpartum pituitary insufficiency, as in Simmonds's syndrome. This seems unlikely, in view of the condition occurring after each of four pregnancies, unless one postulates a limitation of the process to the pituitary mammogenic hormone. The questioner does not indicate whether recurring mastitis has been present, which might have led to progressive fibrosis. A.C.T.H. therapy would not be suitable, because of the numerous side factors of prolonged therapy. Stilboestrol and progesterone might be of help if there were any indications of deficiency of ovarian hormone secretions. It would be interesting also to know whether the patient succeeded in breast-feeding on each occasion. If she did, it would rather suggest that glandular tissue is still present and that the decrease in size of the breasts is due to loss of the supporting fatty tissue, in which case it is doubtful whether anything useful can be done.

Bromidrosis of Scrotum

Q.—*What are the causes and treatment of bromidrosis localized to the scrotum and surrounding parts? My patient, a man of 56, maintains that he "picked it up" during a short stay in hospital.*

A.—It is presumed that there is no disorder of the urinary or gastro-intestinal tracts or local skin disease. Bromidrosis is largely dependent upon general health, and may be related to endocrine or nervous disturbances. Here the affection is probably due to the activity of apocrine glands, and it may be favourably influenced by giving oestrogen as stilboestrol, starting with 1 mg. daily. Local toilet care is important, and the use of a deodorant will help. Bathing with a solution of potassium permanganate (1 in 8,000), bicarbonate of soda (saturated solution), or chlorophyll is suggested.

Oestrogen Therapy of Habitual Abortion

Q.—*In the treatment of a case of habitual abortion, with negative physical findings, I have been advised to give stilboestrol, starting at the sixth week with 5 mg. daily for the first fortnight, and thereafter increasing the dose by 5 mg. daily each fortnight up to the thirty-fourth week. The rationale of this treatment is that a high oestrin level is required to establish a high progesterone level. Will you please comment on this theory? Secondly, are there any dangers in giving such high dosages of stilboestrol for so long?*

A.—It has for long been assumed that habitual abortion is, or may be, due to deficiency of progesterone secretion, particularly at the time of the "change-over" of the site of production from the corpus luteum to the placenta. No convincing evidence for this has ever been adduced. Smith and Smith (see *Physiol. Rev.*, 1948, **28**, 1, for a review) have elaborated a theory that oxidation products of the reversible reaction oestradiol $\rightleftharpoons$ oestrone stimulate the secretion of oestrogen and progesterone, in the non-pregnant woman through the release of pituitary gonadotrophins, and in the pregnant woman through increased utilization of chorionic gonadotrophin. They have further postulated that stilboestrol behaves like the oxidation products in causing an increase in pregnanediol excretion (interpreted as indicative of increased progesterone production) and a fall in serum gonadotrophin (pointing to its increased utilization). Other workers have not been able to confirm these findings. Thus Sommerville, Marrian, and Clayton (*Lancet*, 1949, **1**, 680) found that stilboestrol *decreased* the excretion of pregnanediol, while Loraine (*British Medical Journal*, 1946, **2**, 1496) found that the fall in serum gonadotrophin caused by stilboestrol was merely transient, the level rising again in spite of continued administration of stilboestrol. The theory, therefore, is far from established.

O. W. Smith (*Amer. J. Obstet. Gynec.*, 1948, **56**, 821) claimed that the administration of stilboestrol according to the incremental dosage scheme mentioned in the question gave 77% successful results in the treatment of habitual abortion. Similar results have been obtained with progesterone implants (Bishop and Richards, *British Medical Journal*, 1952, **1**, 244), vitamin E (see Bacharach, *British Medical Journal*, 1940, **1**, 890), and investigation without specific treatment (Bevis, *Lancet*, 1951, **2**, 207). It therefore becomes very doubtful whether these various modes of treatment have any direct effect on the outcome of pregnancy in cases of habitual abortion; if in fact they represent an improvement on the outcome without any attention other than routine antenatal care, it becomes highly probable that their action is mainly psychological.

It is very doubtful if stilboestrol given during pregnancy in the manner considered above produces any harmful effects. There is, however, a report by Meissuer and Sommers (*J. clin. Endocr.*, 1950, **10**, 603) that postpartum endometrial hyperplasia, resulting in prolonged uterine bleeding, has followed the use of stilboestrol and progesterone during pregnancy in diabetics.

Vaginal Discharge in Children

Q.—*How should cases of vaginal discharge in small children (under 5 years) be investigated and treated? What are the commoner causes?*

A.—The scope of this question is so large that it cannot be answered in detail, and reference should be made to Chapters 4 and 5 in *Pediatric Gynecology*, by G. C. Schauffler, 1947, 2nd edition.

Vaginal discharge in infancy is often a true leucorrhoea, consisting of nothing more than desquamated epithelial cells in a serous or muco-serous medium. This is diagnosed by the absence of pus on microscopical examination. It is of no serious significance and requires no treatment other than reassurance of the mother.

On the other hand, the infant's vagina is susceptible to infection, and a purulent discharge is usually the result of vulvo-vaginitis. The gonococcus is the most important, and possibly the commonest, cause of this, but almost any organism may be responsible—the streptococcus, pneumococcus, *Bact. coli*, various fungi, *Trichomonas vaginalis*, etc. The infection arises by direct or indirect contact with other infected individuals—often another child. Predisposing causes are poor general health and lack of cleanliness. Another not uncommon cause of discharge is a foreign body in the vagina or local interference, such as masturbation.

The essential part of the investigation of any case is the examination, both by direct smear and by culture, of discharge obtained from the vagina by a swab or fine pipette gently inserted through the hymeneal opening. If there is any evidence of local interference, or if the discharge resists the usual methods of treatment, it is necessary to carry out an examination under an anaesthetic to exclude the presence of foreign bodies or other lesions in the upper vagina and cervix. Sometimes, however, such possibilities can be excluded by passing a fine female urethroscope into the vagina.

The treatment of vulvo-vaginitis depends to some extent on the organism present and its sensitivity to chemotherapeutic and antibiotic agents. The appropriate one of these should be administered systemically. In non-specific infections the raising of the vaginal resistance by the oral administration of oestrone, 0.3 mg. twice daily for a month, is often helpful, but it may produce side-effects such as enlargement of the breasts and uterine bleeding. Vaginal therapy, either with oestrogens or antiseptics, should be avoided if possible because of its psychological effects. However, occasionally the daily instillation of 0.5% "mercurochrome," or other antiseptic, through a fine rubber catheter is effective when other measures fail. If the vulva is inflamed and sore the child should be kept at rest, and a protective preparation such as zinc and castor oil cream should be applied to the labia minora. Many other considerations arise. These include the need to prevent the child transferring the infection to its eyes and measures to minimize the risk of transfer of the infection to other children. Finally, the general management of the child and its mother is most important. The latter is naturally anxious, and often over-anxious to the extent of exaggeration of the trouble. The former tends to learn surprisingly quickly to take a morbid interest in her complaint and in her genital organs.

Vitamin B Supplements

Q.—*Where can I find information whether vitamin B supplements are necessary for children?*

A.—On p. 151 of the book "*Any Questions?*" The book can be obtained for 7s. 6d. (postage 6d.) from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

NOTES AND COMMENTS

Correction.—Mr. J. A. CHALMERS (Worcester) writes: I have no experience of the Mulvany operation for stress incontinence, as reported on p. 281, August 2. The procedure which I have used with great satisfaction is the Marshall-Marchetti operation of retropubic suspension of the urethra and bladder neck, which is diametrically opposed in its aims to the Mulvany procedure.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.